



Clinical trial results:

A Two-cohort, Open-label, Multicenter Phase II Trial Assessing the Efficacy and Safety of Pertuzumab Given in Combination With Trastuzumab and Vinorelbine in First Line Patients With HER2-positive Advanced (Metastatic or Locally Advanced) Breast Cancer

Summary

EudraCT number	2011-003308-18
Trial protocol	ES IT DE DK
Global end of trial date	15 October 2015

Results information

Result version number	v1 (current)
This version publication date	16 October 2016
First version publication date	16 October 2016

Trial information

Trial identification

Sponsor protocol code	MO27782
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01565083
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 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 November 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this 2-cohort, open-label, multicenter, phase 2 study was overall response rates (ORR), assessed by investigator, of pertuzumab given in combination with trastuzumab (Herceptin) and vinorelbine in first line participants with metastatic or locally advanced human epidermal growth factor receptor (HER) 2-positive breast cancer. Participants received pertuzumab and trastuzumab administered sequentially as separate intravenous (IV) infusions (followed by vinorelbine) and conventional sequential administration of pertuzumab and trastuzumab in separate infusion bags, followed by vinorelbine.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP). Approval from the Independent Ethics Committee/Institutional Review Board (IEC/IRB) was obtained before study start and was documented in a letter to the Investigator specifying the date on which the committee met and granted the approval. The Sponsor also obtained approval from the relevant Competent Authority prior to starting the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 32
Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Italy: 37
Worldwide total number of subjects	213
EEA total number of subjects	154

Notes:

Subjects enrolled per age group

In utero	0
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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)	154
From 65 to 84 years	58
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Due to non-randomized nature of the study (single infusion cohort started enrollment only after separate infusion cohort recruitment was completed) and different baseline characteristics of participants, the comparison between the 2 cohorts was not performed. Hence, the efficacy and safety results for the 2 cohorts should be considered separately.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion
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Arm description:

Pertuzumab IV infusion at a loading dose of 840 milligrams (mg) on Day 1 of Cycle 1 (cycle length = 21 days), followed by 420 mg on Day 1 of each subsequent cycle. Trastuzumab IV infusion at a loading dose of 8 mg per kilogram (mg/kg) on Day 2 of Cycle 1, followed by 6 mg/kg on Day 2 of each subsequent cycle. Vinorelbine IV infusion (administered after trastuzumab) at a dose of 25 mg per meter-squared (mg/m²) on Day 2 and Day 9 of Cycle 1, followed by 30-35 mg/m² on Day 2 and Day 9 of each subsequent cycle. Pertuzumab and trastuzumab were administered sequentially in separate infusion bags, followed by vinorelbine until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end (up to 47 cycles).

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

Dosage and administration details:

Loading dose of 840 mg on Day 1 of first 21-day cycle, followed by 420 mg on Day 1 of each subsequent cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 8 mg/kg on Day 1 of first 21-day cycle, followed by 6 mg/kg on Day 1 or 2 of each subsequent cycle.

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

Dosage and administration details:

A dose of 25 mg/m² followed by 30-35 mg/m² on Days 2 and 9 of the first 21-day cycle and on Days 1 and 8 (or Days 2 and 9) of each subsequent cycle.

Arm title	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion
Arm description:	
Pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (cycle length = 21 days), followed by 420 mg on Day 1 of each subsequent cycle. Trastuzumab IV infusion at a loading dose of 8 mg/kg on Day 2 of Cycle 1, followed by 6 mg/kg on Day 1 of each subsequent cycle. Vinorelbine IV infusion at a dose of 25 mg/m ² on Day 2 and Day 9 of Cycle 1, followed by 30-35 mg/m ² on Day 1 and Day 8 of each subsequent cycle. If administration of all 3 drugs was well tolerated in Cycle 1, then on Day 1 of each subsequent cycle, pertuzumab 420 mg and trastuzumab 6 mg/kg was administered in a single infusion bag, followed by vinorelbine until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end (up to 47 cycles).	
Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 840 mg on Day 1 of first 21-day cycle, followed by 420 mg on Day 1 of each subsequent cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 8 mg/kg on Day 1 of first 21-day cycle, followed by 6 mg/kg on Day 1 or 2 of each subsequent cycle.

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

Dosage and administration details:

A dose of 25 mg/m² followed by 30-35 mg/m² on Days 2 and 9 of the first 21-day cycle and on Days 1 and 8 (or Days 2 and 9) of each subsequent cycle.

Number of subjects in period 1	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion
Started	106	107
Completed	73	68
Not completed	33	39
Consent withdrawn by subject	6	4
Death	22	23
Unspecified	3	5
Lost to follow-up	2	7

Baseline characteristics

Reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion
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Reporting group description:

Pertuzumab IV infusion at a loading dose of 840 milligrams (mg) on Day 1 of Cycle 1 (cycle length = 21 days), followed by 420 mg on Day 1 of each subsequent cycle. Trastuzumab IV infusion at a loading dose of 8 mg per kilogram (mg/kg) on Day 2 of Cycle 1, followed by 6 mg/kg on Day 2 of each subsequent cycle. Vinorelbine IV infusion (administered after trastuzumab) at a dose of 25 mg per meter-squared (mg/m²) on Day 2 and Day 9 of Cycle 1, followed by 30-35 mg/m² on Day 2 and Day 9 of each subsequent cycle. Pertuzumab and trastuzumab were administered sequentially in separate infusion bags, followed by vinorelbine until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end (up to 47 cycles).

Reporting group title	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion
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Reporting group description:

Pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (cycle length = 21 days), followed by 420 mg on Day 1 of each subsequent cycle. Trastuzumab IV infusion at a loading dose of 8 mg/kg on Day 2 of Cycle 1, followed by 6 mg/kg on Day 1 of each subsequent cycle. Vinorelbine IV infusion at a dose of 25 mg/m² on Day 2 and Day 9 of Cycle 1, followed by 30-35 mg/m² on Day 1 and Day 8 of each subsequent cycle. If administration of all 3 drugs was well tolerated in Cycle 1, then on Day 1 of each subsequent cycle, pertuzumab 420 mg and trastuzumab 6 mg/kg was administered in a single infusion bag, followed by vinorelbine until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end (up to 47 cycles).

Reporting group values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion	Total
Number of subjects	106	107	213
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	56.9	55.6	
standard deviation	± 11.8	± 13.17	-
Gender categorical Units: Subjects			
Female	106	106	212
Male	0	1	1

End points

End points reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion
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Reporting group description:

Pertuzumab IV infusion at a loading dose of 840 milligrams (mg) on Day 1 of Cycle 1 (cycle length = 21 days), followed by 420 mg on Day 1 of each subsequent cycle. Trastuzumab IV infusion at a loading dose of 8 mg per kilogram (mg/kg) on Day 2 of Cycle 1, followed by 6 mg/kg on Day 2 of each subsequent cycle. Vinorelbine IV infusion (administered after trastuzumab) at a dose of 25 mg per meter-squared (mg/m²) on Day 2 and Day 9 of Cycle 1, followed by 30-35 mg/m² on Day 2 and Day 9 of each subsequent cycle. Pertuzumab and trastuzumab were administered sequentially in separate infusion bags, followed by vinorelbine until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end (up to 47 cycles).

Reporting group title	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion
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Reporting group description:

Pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (cycle length = 21 days), followed by 420 mg on Day 1 of each subsequent cycle. Trastuzumab IV infusion at a loading dose of 8 mg/kg on Day 2 of Cycle 1, followed by 6 mg/kg on Day 1 of each subsequent cycle. Vinorelbine IV infusion at a dose of 25 mg/m² on Day 2 and Day 9 of Cycle 1, followed by 30-35 mg/m² on Day 1 and Day 8 of each subsequent cycle. If administration of all 3 drugs was well tolerated in Cycle 1, then on Day 1 of each subsequent cycle, pertuzumab 420 mg and trastuzumab 6 mg/kg was administered in a single infusion bag, followed by vinorelbine until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end (up to 47 cycles).

Subject analysis set title	Intent-to-treat (ITT) population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

ITT population included all participants enrolled into the study was used for all analyses in this study.

Primary: Percentage of Participants With Best Overall Response (BOR) as Assessed by Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Percentage of Participants With Best Overall Response (BOR) as Assessed by Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) ^[1]
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End point description:

Tumor response was assessed by investigator according to RECIST v1.1. BOR was defined as percentage of participants with a confirmed complete response (CR) or partial response (PR). All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total or pathological nodes (with short axis [SA] of at least ($\geq$) 15 millimeter [mm]) were identified as target lesions (TLs) and measured and recorded at baseline. A sum of diameters (longest for non-nodal lesions, SA for nodal lesions) for all TLs was calculated and reported as baseline sum of diameters (SD). All other lesions (or sites of disease) were identified as non-TLs. CR: disappearance of all TLs and SA reduction to less than ($<$) 10 mm for nodal TLs/ non-TLs. PR: $\geq$ 30 percent (%) decrease in SD of TLs, taking as reference baseline SD. Confirmation of response at 2 consecutive tumor assessments $\geq$ 4 weeks apart was required. The 95% confidence interval (CI) was computed using Clopper-Pearson approach. ITT population.

End point type	Primary
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End point timeframe:

Baseline, every 3 cycles up to 36 months, and every 6 cycles thereafter if progression free after 36 months, 28 days after end of treatment, every 3 months thereafter (maximum up to approximately 3.5 years)

Notes:

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

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

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89 ^[2]	91 ^[3]		
Units: percentage of participants				
number (confidence interval 95%)	74.2 (63.8 to 82.9)	63.7 (53 to 73.6)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response as Assessed by Investigator According to RECIST v 1.1

End point title	Time to Response as Assessed by Investigator According to RECIST v 1.1
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End point description:

For participants with a BOR of CR or PR, time to response = (Date of first confirmed CR/PR - Date of first study treatment) + 1. For participants without a CR or PR, time to response = (Date of adequate last tumor assessment - Date of first study treatment) + 1. For participant with no tumor assessment (or if all assessments were progressive disease [PD]) the censoring day was set to date of first study treatment +1. CR: the disappearance of all TLs and SA reduction to <10 mm for nodal TLs/ non-TLs. PR: $\geq 30\%$ decrease in SD of TLs, taking as reference the baseline SD. Confirmation of response at 2 consecutive tumor assessments ≥ 4 weeks apart was required. PD: $\geq 20\%$ relative increase and ≥ 5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. The 95% CI was computed using log-log transformation. ITT population.

End point type	Secondary
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End point timeframe:

Baseline, every 3 cycles up to 36 months, and every 6 cycles thereafter if progression free after 36 months, 28 days after end of treatment, every 3 months thereafter (maximum up to approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89 ^[4]	91 ^[5]		
Units: months				
median (confidence interval 95%)	2.1 (2 to 2.2)	2.2 (2.1 to 4.4)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Assessed by Investigator According to RECIST v 1.1

End point title	Duration of Response (DOR) as Assessed by Investigator According to RECIST v 1.1
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End point description:

DOR in participants with a BOR of CR or PR, was defined as the period from date of initial PR or CR until date of PD or death from any cause. Participants with no documented PD or death after CR or PR were censored at last date at which they were known to have had the CR or PR, respectively (regardless of the response at intermediate assessments). CR: disappearance of all TLs and SA reduction to <10 mm for nodal TLs/ non-TLs. PR: $\geq 30\%$ decrease in SD of TLs, taking as reference the baseline SD. Confirmation of response at 2 consecutive tumor assessments ≥ 4 weeks apart was required. PD: $\geq 20\%$ relative increase and ≥ 5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. The 95% CI was computed using log-log transformation. ITT population. Only participants with a BOR of CR or PR and with measurable disease at baseline were included in the analysis.

End point type	Secondary
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End point timeframe:

Baseline, every 3 cycles up to 36 months, and every 6 cycles thereafter if progression free after 36 months, 28 days after end of treatment, every 3 months thereafter (maximum up to approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	58		
Units: months				
median (confidence interval 95%)	13.3 (10.6 to 16.2)	11.8 (7.5 to 17.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Progression as Assessed by Investigator According to RECIST v1.1 or Death From any Cause

End point title	Percentage of Participants With Disease Progression as Assessed by Investigator According to RECIST v1.1 or Death From any Cause
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End point description:

PD was defined as $\geq 20\%$ relative increase and ≥ 5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. Percentage of participants with radio-graphically documented PD as assessed by investigator according to RECIST v1.1 or death due to any cause was reported. ITT population.

End point type	Secondary
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End point timeframe:

Baseline, every 3 cycles up to 36 months, and every 6 cycles thereafter if progression free after 36 months, 28 days after end of treatment, every 3 months thereafter (maximum up to approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	107		
Units: percentage of participants				
number (not applicable)	69.8	67.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) as Assessed by Investigator According to RECIST v 1.1

End point title	Progression-free Survival (PFS) as Assessed by Investigator According to RECIST v 1.1
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End point description:

PFS was defined as the time from first intake of any study medication until the first radio-graphically documented PD as assessed by investigator according to RECIST v1.1 or death due to any cause, whichever occurred first. Participants with no PFS events were censored at the time of the last evaluable tumor assessment. Participants with no baseline or no tumor assessment after the baseline visit were censored on the date of first study treatment. PD: $\geq 20\%$ relative increase and ≥ 5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. Participants who had radio-graphically documented PD as assessed by investigator according to RECIST v1.1 or died due to any cause were considered as having an event. The median PFS was estimated using Kaplan-Meier method. The 95% CI was computed using log-log transformation. ITT population.

End point type	Secondary
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End point timeframe:

Baseline, every 3 cycles up to 36 months, and every 6 cycles thereafter if progression free after 36 months, 28 days after end of treatment, every 3 months thereafter (maximum up to approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	107		
Units: months				
median (confidence interval 95%)	14.3 (11.2 to 17.5)	11.5 (10.3 to 15.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Progression as Assessed by Investigator According to RECIST v1.1

End point title	Percentage of Participants With Disease Progression as Assessed by Investigator According to RECIST v1.1
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End point description:

PD was defined as $\geq 20\%$ relative increase and ≥ 5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. Percentage of participants with radio-graphically documented PD as assessed by investigator according to RECIST v1.1 was reported. ITT population.

End point type	Secondary
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End point timeframe:

Baseline, every 3 cycles up to 36 months, and every 6 cycles thereafter if progression free after 36 months, 28 days after end of treatment, every 3 months thereafter (maximum up to approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	107		
Units: percentage of participants				
number (not applicable)	67.9	61.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) as Assessed by Investigator According to RECIST v 1.1

End point title	Time to Progression (TTP) as Assessed by Investigator According to RECIST v 1.1
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End point description:

TTP was defined as the time from first intake of any study medication until the first radio-graphically documented PD as assessed by investigator according to RECIST v1.1. Participants who did not have a radio-graphically documented PD and had died due to reason other than PD were censored on the last available tumor assessment prior to the death date. Participants with no baseline or no tumor assessment after the baseline visit were censored on the date of first study treatment. PD: $\geq 20\%$ relative increase and ≥ 5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. Participants who had radio-graphically documented PD as assessed by investigator according to RECIST v1.1 were considered as having an event. The median TTP was estimated using Kaplan-Meier method. The 95% CI was computed using log-log transformation. ITT population.

End point type	Secondary
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End point timeframe:

Baseline, every 3 cycles up to 36 months, and every 6 cycles thereafter if progression free after 36 months, 28 days after end of treatment, every 3 months thereafter (maximum up to approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	107		
Units: months				
median (confidence interval 95%)	14.9 (11.3 to 17.9)	12.8 (10.4 to 17.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died From any Cause

End point title	Percentage of Participants Who Died From any Cause
End point description:	Percentage of participants who died due to any cause was reported. ITT population.
End point type	Secondary
End point timeframe:	Baseline until death (up to approximately 3.5 years)

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	107		
Units: percentage of participants				
number (not applicable)	21.7	21.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	OS was defined as the time from first intake of any study medication to the date of death, regardless of the cause of death. Participants who were known to be alive at the time of the analysis were censored at the date of the last follow-up assessment. Participants without follow-up assessment were censored at

the day of last study treatment, and participants with no post-baseline information were censored at the date of first study treatment plus 1 day. Participants who died due to any cause were considered as having an event. The median OS was estimated using Kaplan-Meier method. The 95% CI was computed using log-log transformation. ITT population. The data '99999 (99999 to 99999)' in the results signifies that median and corresponding CI could not be calculated due to low number of participants who had an event.

End point type	Secondary
End point timeframe:	
Baseline until death (up to approximately 3.5 years)	

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	107		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Quality of Life-5 Dimensions (EQ-5D) Questionnaire Visual Analogue Scale (VAS) Score

End point title	Change from Baseline in European Quality of Life-5 Dimensions (EQ-5D) Questionnaire Visual Analogue Scale (VAS) Score
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End point description:

EQ-5D VAS: participant rated questionnaire to assess health-related quality of life (QoL) in terms of a single index value. The VAS component rates current health state on a scale from 0 mm (worst imaginable health state) to 100 mm (best imaginable health state); higher scores indicate a better health state. ITT population. Here, 'Number of subjects analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point. The data '99999' in the results signifies that either mean was not available because no participant was evaluable at indicated time points or standard deviation was not available because only 1 participant was evaluable at indicated time points.

End point type	Secondary
End point timeframe:	
Baseline, thereafter every 3 cycles from Cycle 3 to Cycle 45 (each cycle = 21 days)	

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	102		
Units: units on a scale				

arithmetic mean (standard deviation)				
Baseline (n = 102, 102)	69.7 (± 22.74)	68.6 (± 23.58)		
Change at Cycle 3 (n = 83, 90)	0.9 (± 19.31)	1.7 (± 23.16)		
Change at Cycle 6 (n= 68, 82)	1 (± 23.59)	4.3 (± 24.49)		
Change at Cycle 9 (n= 67, 68)	2.2 (± 23)	6.6 (± 26.29)		
Change at Cycle 12 (n= 53, 59)	-1.4 (± 30.19)	6.8 (± 23.59)		
Change at Cycle 15 (n= 43, 43)	6.3 (± 19.34)	8.1 (± 24.45)		
Change at Cycle 18 (n=32, 28)	5.7 (± 21.83)	6.5 (± 22.12)		
Change at Cycle 21 (n= 30, 27)	3.2 (± 20)	1.3 (± 28.5)		
Change at Cycle 24 (n= 25, 26)	3.1 (± 17.06)	2.8 (± 23.16)		
Change at Cycle 27 (n= 21, 24)	5.9 (± 18.79)	1.1 (± 20.16)		
Change at Cycle 30 (n= 18, 19)	5.4 (± 19.87)	9.5 (± 19.68)		
Change at Cycle 33 (n= 15, 15)	2.9 (± 24.03)	13.4 (± 19.65)		
Change at Cycle 36 (n=14, 7)	4.8 (± 17.37)	7.3 (± 21.72)		
Change at Cycle 39 (n=6, 1)	15.8 (± 19.85)	50 (± 99999)		
Change at Cycle 42 (n= 2, 0)	-5 (± 14.14)	99999 (± 99999)		
Change at Cycle 45 (n= 1, 0)	5 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Cancer Therapy-Breast (FACT-B) Questionnaire Score

End point title	Change from Baseline in Functional Assessment of Cancer Therapy-Breast (FACT-B) Questionnaire Score
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End point description:

FACT-B questionnaire is used for assessment of health-related QoL in participants with breast cancer. It consists of 36 items, summarized to 5 subscales: physical (7 items), functional (7 items), social/family (7 items); all 3 ranged from 0 to 28, emotional (6 items) ranging from 0 to 24, and breast cancer subscale (9 items) ranging from 0 to 36; high subscale score represents a better QoL. All single-item measures ranges from 0='Not at all' to 4='Very much'. Total possible score ranged from 0 to 144. High scale score represents a better QoL. ITT population. Here, 'Number of subjects analysed' signifies the number of participants evaluable for this outcome measure and 'n' signifies the number of participants evaluable at specified time point. The data '99999' in the results signifies that either mean was not available because no participant was evaluable or standard deviation was not available because only 1 participant was evaluable at indicated time points.

End point type	Secondary
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End point timeframe:

Baseline, thereafter every 3 cycles from Cycle 3 to Cycle 45 (each cycle = 21 days)

End point values	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	100		
Units: units on a scale				

arithmetic mean (standard deviation)				
Baseline (n = 100, 100)	76.7 (± 13.46)	78.5 (± 16.06)		
Change at Cycle 3 (n = 82, 90)	-1.96 (± 10.872)	-2.57 (± 13.159)		
Change at Cycle 6 (n= 70, 79)	-0.97 (± 12.749)	0.47 (± 13.724)		
Change at Cycle 9 (n= 65, 60)	1.44 (± 13.189)	-0.42 (± 14.602)		
Change at Cycle 12 (n= 52, 51)	0.4 (± 12.057)	0.51 (± 14.51)		
Change at Cycle 15 (n= 43, 44)	2.72 (± 10.989)	0.09 (± 13.713)		
Change at Cycle 18 (n= 32, 32)	4.58 (± 11.801)	0.51 (± 16.512)		
Change at Cycle 21 (n= 29, 24)	3.22 (± 13.178)	-0.23 (± 16.116)		
Change at Cycle 24 (n= 26, 23)	1.19 (± 10.66)	-1.03 (± 14.546)		
Change at Cycle 27 (n= 20, 22)	4.91 (± 9.9)	0.55 (± 14.185)		
Change at Cycle 30 (n= 18, 24)	3.96 (± 11.082)	-0.26 (± 17.381)		
Change at Cycle 33 (n= 14, 17)	5.75 (± 13.272)	1.76 (± 19.179)		
Change at Cycle 36 (n= 15, 13)	1.26 (± 9.21)	2.74 (± 14.354)		
Change at Cycle 39 (n= 6, 6)	-3.68 (± 16.866)	7.33 (± 20.992)		
Change at Cycle 42 (n= 4, 0)	-0.17 (± 10.599)	99999 (± 99999)		
Change at Cycle 45 (n= 1, 0)	1 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 until 28 days after last study treatment (up to approximately 3.5 years)

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) are adverse events occurring between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pre-treatment state. Safety Population included all participants who received at least one dose of any study treatment in any of the 2 cohorts.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion
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Reporting group description:

Pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (cycle length = 21 days), followed by 420 mg on Day 1 of each subsequent cycle. Trastuzumab IV infusion at a loading dose of 8 mg/kg on Day 2 of Cycle 1, followed by 6 mg/kg on Day 2 of each subsequent cycle. Vinorelbine IV infusion (administered after trastuzumab) at a dose of 25 mg/m² on Day 2 and Day 9 of Cycle 1, followed by 30-35 mg/m² on Day 2 and Day 9 of each subsequent cycle. Pertuzumab and trastuzumab were administered sequentially in separate infusion bags, followed by vinorelbine until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end (up to 47 cycles).

Reporting group title	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion
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Reporting group description:

Pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (cycle length = 21 days), followed by 420 mg on Day 1 of each subsequent cycle. Trastuzumab IV infusion at a loading dose of 8 mg/kg on Day 2 of Cycle 1, followed by 6 mg/kg on Day 1 of each subsequent cycle. Vinorelbine IV infusion at a dose of 25 mg/m² on Day 2 and Day 9 of Cycle 1, followed by 30-35 mg/m² on Day 1 and Day 8 of each subsequent cycle. If administration of all 3 drugs was well tolerated in Cycle 1, then on Day 1 of each subsequent cycle, pertuzumab 420 mg and trastuzumab 6 mg/kg was administered in a single infusion bag, followed by vinorelbine until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end (up to 47 cycles).

Serious adverse events	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 106 (30.19%)	44 / 107 (41.12%)	
number of deaths (all causes)	23	23	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malignant melanoma			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 106 (0.94%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 106 (0.94%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 106 (1.89%)	6 / 107 (5.61%)	
occurrences causally related to treatment / all	1 / 2	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	2 / 106 (1.89%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	5 / 106 (4.72%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 106 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 106 (0.94%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 106 (0.94%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
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	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paraparesis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensorimotor disorder			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
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			
Febrile neutropenia			
subjects affected / exposed	6 / 106 (5.66%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	6 / 7	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 106 (0.94%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia obstructive			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 106 (1.89%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 106 (0.94%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			

subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 106 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	0 / 106 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
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	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 106 (0.94%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nosocomial infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	2 / 106 (1.89%)	4 / 107 (3.74%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	3 / 3	
Sepsis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 106 (1.89%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pertuzumab + Trastuzumab + Vinorelbine: Separate Infusion	Pertuzumab + Trastuzumab + Vinorelbine: Single Infusion	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 106 (97.17%)	106 / 107 (99.07%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	7 / 106 (6.60%)	5 / 107 (4.67%)	
occurrences (all)	8	6	
Hypertension			
subjects affected / exposed	8 / 106 (7.55%)	31 / 107 (28.97%)	
occurrences (all)	11	85	
Hypotension			

subjects affected / exposed occurrences (all)	6 / 106 (5.66%) 9	3 / 107 (2.80%) 3	
Phlebitis subjects affected / exposed occurrences (all)	3 / 106 (2.83%) 5	8 / 107 (7.48%) 9	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	42 / 106 (39.62%) 81	29 / 107 (27.10%) 48	
Chest pain subjects affected / exposed occurrences (all)	7 / 106 (6.60%) 8	10 / 107 (9.35%) 12	
Chills subjects affected / exposed occurrences (all)	30 / 106 (28.30%) 37	14 / 107 (13.08%) 16	
Extravasation subjects affected / exposed occurrences (all)	1 / 106 (0.94%) 1	7 / 107 (6.54%) 7	
Fatigue subjects affected / exposed occurrences (all)	36 / 106 (33.96%) 63	41 / 107 (38.32%) 73	
Influenza like illness subjects affected / exposed occurrences (all)	7 / 106 (6.60%) 10	9 / 107 (8.41%) 10	
Mucosal inflammation subjects affected / exposed occurrences (all)	16 / 106 (15.09%) 31	26 / 107 (24.30%) 33	
Oedema peripheral subjects affected / exposed occurrences (all)	6 / 106 (5.66%) 8	13 / 107 (12.15%) 16	
Pain subjects affected / exposed occurrences (all)	7 / 106 (6.60%) 10	12 / 107 (11.21%) 18	
Pyrexia			

subjects affected / exposed occurrences (all)	35 / 106 (33.02%) 56	22 / 107 (20.56%) 28	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	6 / 106 (5.66%) 7	4 / 107 (3.74%) 4	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	18 / 106 (16.98%) 24	24 / 107 (22.43%) 31	
Dyspnoea subjects affected / exposed occurrences (all)	12 / 106 (11.32%) 15	26 / 107 (24.30%) 34	
Epistaxis subjects affected / exposed occurrences (all)	14 / 106 (13.21%) 19	21 / 107 (19.63%) 25	
Nasal dryness subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 3	6 / 107 (5.61%) 7	
Nasal inflammation subjects affected / exposed occurrences (all)	3 / 106 (2.83%) 3	8 / 107 (7.48%) 11	
Oropharyngeal pain subjects affected / exposed occurrences (all)	13 / 106 (12.26%) 17	5 / 107 (4.67%) 6	
Rhinorrhoea subjects affected / exposed occurrences (all)	5 / 106 (4.72%) 5	7 / 107 (6.54%) 9	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 2	10 / 107 (9.35%) 12	
Depression subjects affected / exposed occurrences (all)	10 / 106 (9.43%) 11	8 / 107 (7.48%) 12	
Insomnia			

subjects affected / exposed occurrences (all)	10 / 106 (9.43%) 10	19 / 107 (17.76%) 24	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	8 / 106 (7.55%) 15	11 / 107 (10.28%) 18	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	4 / 106 (3.77%) 5	10 / 107 (9.35%) 12	
Ejection fraction decreased subjects affected / exposed occurrences (all)	9 / 106 (8.49%) 17	2 / 107 (1.87%) 2	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	9 / 106 (8.49%) 11	9 / 107 (8.41%) 13	
Weight decreased subjects affected / exposed occurrences (all)	22 / 106 (20.75%) 23	22 / 107 (20.56%) 31	
Weight increased subjects affected / exposed occurrences (all)	1 / 106 (0.94%) 1	6 / 107 (5.61%) 6	
Injury, poisoning and procedural complications			
Radiation skin injury subjects affected / exposed occurrences (all)	1 / 106 (0.94%) 1	6 / 107 (5.61%) 8	
Cardiac disorders			
Tachycardia subjects affected / exposed occurrences (all)	3 / 106 (2.83%) 3	7 / 107 (6.54%) 7	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	4 / 106 (3.77%) 4	16 / 107 (14.95%) 19	
Dysgeusia			

subjects affected / exposed	9 / 106 (8.49%)	8 / 107 (7.48%)	
occurrences (all)	9	11	
Headache			
subjects affected / exposed	15 / 106 (14.15%)	27 / 107 (25.23%)	
occurrences (all)	18	55	
Neuropathy peripheral			
subjects affected / exposed	11 / 106 (10.38%)	23 / 107 (21.50%)	
occurrences (all)	14	33	
Paraesthesia			
subjects affected / exposed	20 / 106 (18.87%)	9 / 107 (8.41%)	
occurrences (all)	32	18	
Peripheral sensory neuropathy			
subjects affected / exposed	9 / 106 (8.49%)	10 / 107 (9.35%)	
occurrences (all)	11	12	
Polyneuropathy			
subjects affected / exposed	5 / 106 (4.72%)	8 / 107 (7.48%)	
occurrences (all)	7	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	36 / 106 (33.96%)	19 / 107 (17.76%)	
occurrences (all)	87	30	
Leukopenia			
subjects affected / exposed	24 / 106 (22.64%)	16 / 107 (14.95%)	
occurrences (all)	108	62	
Neutropenia			
subjects affected / exposed	54 / 106 (50.94%)	61 / 107 (57.01%)	
occurrences (all)	183	197	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 106 (1.89%)	6 / 107 (5.61%)	
occurrences (all)	2	8	
Lacrimation increased			
subjects affected / exposed	6 / 106 (5.66%)	6 / 107 (5.61%)	
occurrences (all)	6	7	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	15 / 106 (14.15%)	19 / 107 (17.76%)	
occurrences (all)	21	24	
Abdominal pain upper			
subjects affected / exposed	20 / 106 (18.87%)	22 / 107 (20.56%)	
occurrences (all)	23	30	
Constipation			
subjects affected / exposed	35 / 106 (33.02%)	35 / 107 (32.71%)	
occurrences (all)	45	47	
Diarrhoea			
subjects affected / exposed	61 / 106 (57.55%)	62 / 107 (57.94%)	
occurrences (all)	144	179	
Dry mouth			
subjects affected / exposed	2 / 106 (1.89%)	7 / 107 (6.54%)	
occurrences (all)	2	9	
Dyspepsia			
subjects affected / exposed	7 / 106 (6.60%)	15 / 107 (14.02%)	
occurrences (all)	9	20	
Haemorrhoids			
subjects affected / exposed	9 / 106 (8.49%)	4 / 107 (3.74%)	
occurrences (all)	15	4	
Nausea			
subjects affected / exposed	52 / 106 (49.06%)	44 / 107 (41.12%)	
occurrences (all)	98	78	
Stomatitis			
subjects affected / exposed	19 / 106 (17.92%)	26 / 107 (24.30%)	
occurrences (all)	31	37	
Vomiting			
subjects affected / exposed	34 / 106 (32.08%)	25 / 107 (23.36%)	
occurrences (all)	62	32	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	27 / 106 (25.47%)	28 / 107 (26.17%)	
occurrences (all)	31	29	
Dry skin			

subjects affected / exposed occurrences (all)	7 / 106 (6.60%) 7	12 / 107 (11.21%) 13	
Erythema subjects affected / exposed occurrences (all)	9 / 106 (8.49%) 11	3 / 107 (2.80%) 3	
Nail disorder subjects affected / exposed occurrences (all)	6 / 106 (5.66%) 6	6 / 107 (5.61%) 6	
Onychoclasia subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 2	8 / 107 (7.48%) 8	
Pruritus subjects affected / exposed occurrences (all)	12 / 106 (11.32%) 13	9 / 107 (8.41%) 9	
Rash subjects affected / exposed occurrences (all)	25 / 106 (23.58%) 38	12 / 107 (11.21%) 15	
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	3 / 106 (2.83%) 3	7 / 107 (6.54%) 7	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	18 / 106 (16.98%) 24	16 / 107 (14.95%) 22	
Back pain subjects affected / exposed occurrences (all)	18 / 106 (16.98%) 24	27 / 107 (25.23%) 31	
Bone pain subjects affected / exposed occurrences (all)	13 / 106 (12.26%) 14	7 / 107 (6.54%) 13	
Muscle spasms subjects affected / exposed occurrences (all)	21 / 106 (19.81%) 25	28 / 107 (26.17%) 38	
Myalgia			

subjects affected / exposed occurrences (all)	20 / 106 (18.87%) 26	11 / 107 (10.28%) 11	
Neck pain subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 2	6 / 107 (5.61%) 7	
Pain in extremity subjects affected / exposed occurrences (all)	14 / 106 (13.21%) 19	29 / 107 (27.10%) 43	
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	8 / 106 (7.55%) 11	3 / 107 (2.80%) 3	
Cystitis subjects affected / exposed occurrences (all)	8 / 106 (7.55%) 11	16 / 107 (14.95%) 22	
Gastroenteritis subjects affected / exposed occurrences (all)	6 / 106 (5.66%) 7	3 / 107 (2.80%) 4	
Influenza subjects affected / exposed occurrences (all)	11 / 106 (10.38%) 12	4 / 107 (3.74%) 5	
Nasopharyngitis subjects affected / exposed occurrences (all)	20 / 106 (18.87%) 32	15 / 107 (14.02%) 29	
Paronychia subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 3	6 / 107 (5.61%) 12	
Rhinitis subjects affected / exposed occurrences (all)	14 / 106 (13.21%) 16	7 / 107 (6.54%) 7	
Sinusitis subjects affected / exposed occurrences (all)	4 / 106 (3.77%) 4	7 / 107 (6.54%) 10	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 106 (4.72%) 6	15 / 107 (14.02%) 18	

Urinary tract infection subjects affected / exposed occurrences (all)	11 / 106 (10.38%) 16	13 / 107 (12.15%) 17	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	23 / 106 (21.70%) 27	24 / 107 (22.43%) 27	
Hypocalcaemia subjects affected / exposed occurrences (all)	6 / 106 (5.66%) 15	5 / 107 (4.67%) 5	
Hypokalaemia subjects affected / exposed occurrences (all)	7 / 106 (6.60%) 10	5 / 107 (4.67%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2012	- As MO27782 was an open-label study, words referring to randomization were removed and/or replaced - The study treatment administration scheme was corrected - The algorithm for continuation and discontinuation of pertuzumab and trastuzumab based on left ventricular ejection fraction (LVEF) assessments were revised in order to be consistent with the baseline LVEF criteria of $\geq 55\%$ - Clarification of several exclusion criteria - Clarification of the role of the IDMC - Changes to the prior and concomitant medications and therapies - Change to the time of the final analysis of primary endpoint
23 January 2013	- Clarification of the timing of the IDMC review - Inclusion of participants who had received hormonal therapy. To reflect the current use of hormonal therapies and everolimus in the participant population, the protocol was amended to allow inclusion of participants who, prior to study entry had received up to two lines of hormonal therapies for metastatic or locally recurrent disease, one of which could have been in combination with everolimus - Inclusion of participants with central nervous system (CNS) metastases, if the CNS metastases were medically well controlled prior to screening (as assessed by the investigator) after receiving local therapy (irradiation, surgery, etc) but without anti-Human Epidermal Growth Factor Receptor (HER) 2 therapy - Clarification of several exclusion criteria (including the exclusion of participants with cardiac disorders at risk of a serious adverse event) - Endpoint assessment and study end. Modification to timing of final assessment of ORR to enable timely results, rather than an open-ended final assessment time. Clarification of OS analysis timing and end of study - Infusion times and scheduling. New instructions introduced to enable appropriate monitoring of safety during initial pertuzumab/trastuzumab infusions - Abnormal liver values. New section introduced providing guidance on abnormal liver values, as required by updated Roche protocol template - Clarification of coagulation testing and HER2 status assessments
20 January 2014	- Removal of the use of the Independent Review Committee to assess the primary endpoint. Amended to "the primary endpoint to include ORR as assessed by the Investigator" - Analysis sections updated to ensure an accurate description of data evaluation. Efficacy endpoints were to be presented by each cohort with an exploratory comparison between cohorts only - Pregnancy follow-up. Increased pregnancy follow-up, restrictions on breastfeeding and use of adequate contraception to 7 months following last dose of study medication, in line with changes to recommendations given in trastuzumab labeling - Scope of interim review. Defined to reflect that efficacy data were to have been provided if requested by the IDMC, as outlined in the IDMC charter - Definition of secondary variables (time to response, duration of response, PFS, time to progression and overall survival) were amended to be measured as time from first intake of study medication rather than time from date of enrollment as this provided a more accurate measure of these endpoints. Documentation of PFS was broadened to include the option of pathological diagnosis of progression

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported