Clinical trial results:
An Exploratory Phase II, Single Arm, Multicenter Study to Evaluate the Efficacy and Safety of the Combination of Pertuzumab and Herceptin (Trastuzumab) in Patients With HER2-Positive Metastatic Breast Cancer

Summary

EudraCT number	2005-003493-19
Trial protocol	GB IT ES
Global end of trial date	01 September 2015

Results information

Result version number	v1 (current)
This version publication date	05 August 2016
First version publication date	05 August 2016

Trial information

Trial identification

Sponsor protocol code	BO17929

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01674062
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	02 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to make a preliminary assessment of the efficacy of pertuzumab in combination with trastuzumab in participants who have progressed on trastuzumab-based therapy, as determined by the objective response (OR) rate and/or the clinical benefit response (CBR) rate. Country of study site was known for 93 of the 95 enrolled/treated participants; thus, the 2 remaining individuals have been categorized under Canada (26 participants confirmed).

Protection of trial subjects:

The investigator has 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 must have fully adhered to the principles outlined in the Guideline for Good Clinical Practice International Council for Harmonisation (ICH) Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the participant. In other countries where the Guideline for Good Clinical Practice exists, Roche and the investigators have strictly ensured adherence to the stated provisions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 May 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	9 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	Spain: 20
Worldwide total number of subjects	95
EEA total number of subjects	67

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)	80
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 99 participants with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer were screened for Cohorts 1 and 2, of whom 66 were recruited. Following primary analysis of Cohorts 1 and 2, a total of 51 new participants were screened for Cohort 3, of whom 29 were recruited.

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
Arm title	Pertuzumab + Trastuzumab (Cohorts 1 and 2)

Arm description:

Females with HER2-positive metastatic breast cancer received dual-agent treatment with pertuzumab and trastuzumab. Recruitment for Cohorts 1 and 2 was conducted separately; however, the same regimen was administered to both sets of participants. Trastuzumab was administered via intravenous (IV) infusion as 2 milligrams per kilogram (mg/kg) once weekly, or as 6 mg/kg every 3 weeks, beginning on Day 1 of Cycle 1. Pertuzumab was administered via IV infusion at a loading dose of 840 milligrams (mg) followed by a standard dose of 420 mg every 3 weeks, beginning on Day 2 of Cycle 1. Thereafter, both medications were administered on Day 1 of each 3-week cycle. Treatment continued for a minimum of 8 cycles and could be extended until disease progression, intolerable toxicity, or death.

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

Dosage and administration details:

Pertuzumab was administered via IV infusion at a loading dose of 840 mg followed by a standard dose of 420 mg every 3 weeks. Treatment could continue until disease progression, intolerable toxicity, or death.

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

Dosage and administration details:

Trastuzumab was administered via IV infusion as 2 mg/kg once weekly, or as 6 mg/kg every 3 weeks. Treatment could continue until disease progression, intolerable toxicity, or death.

Arm title	Pertuzumab +/- Trastuzumab (Cohort 3)

Arm description:

Females with HER2-positive metastatic breast cancer received single-agent treatment with pertuzumab. Recruitment for Cohort 3 was conducted following primary analysis of Cohorts 1 and 2. Pertuzumab was administered via IV infusion at a loading dose of 840 mg followed by a standard dose of 420 mg every 3 weeks, administered on Day 1 of each 3-week cycle. Participants with documented disease progression could have trastuzumab added to the regimen, per the dosing schedule described for Cohorts 1 and 2, to receive dual-agent treatment until disease progression, intolerable toxicity, or death.

Arm type	Experimental

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

Dosage and administration details:

Pertuzumab was administered via IV infusion at a loading dose of 840 mg followed by a standard dose of 420 mg every 3 weeks. Treatment could continue until disease progression, intolerable toxicity, or death.

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

Dosage and administration details:

Trastuzumab was administered via IV infusion as 2 mg/kg once weekly, or as 6 mg/kg every 3 weeks. Treatment could continue until disease progression, intolerable toxicity, or death.

Number of subjects in period 1	Pertuzumab + Trastuzumab (Cohorts 1 and 2)	Pertuzumab +/- Trastuzumab (Cohort 3)
Started	66	29
Completed	0	0
Not completed	66	29
Insufficient therapeutic response	56	26
Death	-	1
Not specified	8	1
Adverse event	1	1
Programming error	1	-

Baseline characteristics

Reporting groups

Reporting group title	Pertuzumab + Trastuzumab (Cohorts 1 and 2)

Reporting group description:

Females with HER2-positive metastatic breast cancer received dual-agent treatment with pertuzumab and trastuzumab. Recruitment for Cohorts 1 and 2 was conducted separately; however, the same regimen was administered to both sets of participants. Trastuzumab was administered via intravenous (IV) infusion as 2 milligrams per kilogram (mg/kg) once weekly, or as 6 mg/kg every 3 weeks, beginning on Day 1 of Cycle 1. Pertuzumab was administered via IV infusion at a loading dose of 840 milligrams (mg) followed by a standard dose of 420 mg every 3 weeks, beginning on Day 2 of Cycle 1. Thereafter, both medications were administered on Day 1 of each 3-week cycle. Treatment continued for a minimum of 8 cycles and could be extended until disease progression, intolerable toxicity, or death.

Reporting group title	Pertuzumab +/- Trastuzumab (Cohort 3)

Reporting group description:

Females with HER2-positive metastatic breast cancer received single-agent treatment with pertuzumab. Recruitment for Cohort 3 was conducted following primary analysis of Cohorts 1 and 2. Pertuzumab was administered via IV infusion at a loading dose of 840 mg followed by a standard dose of 420 mg every 3 weeks, administered on Day 1 of each 3-week cycle. Participants with documented disease progression could have trastuzumab added to the regimen, per the dosing schedule described for Cohorts 1 and 2, to receive dual-agent treatment until disease progression, intolerable toxicity, or death.

Reporting group values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)	Pertuzumab +/- Trastuzumab (Cohort 3)	Total
Number of subjects	66	29	95
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.9	53	
standard deviation	± 12.6	± 7.95	-
Gender categorical Units: Subjects			
Female	66	29	95
Male	0	0	0

End points

End points reporting groups

Reporting group title	Pertuzumab + Trastuzumab (Cohorts 1 and 2)

Reporting group description:

Females with HER2-positive metastatic breast cancer received dual-agent treatment with pertuzumab and trastuzumab. Recruitment for Cohorts 1 and 2 was conducted separately; however, the same regimen was administered to both sets of participants. Trastuzumab was administered via intravenous (IV) infusion as 2 milligrams per kilogram (mg/kg) once weekly, or as 6 mg/kg every 3 weeks, beginning on Day 1 of Cycle 1. Pertuzumab was administered via IV infusion at a loading dose of 840 milligrams (mg) followed by a standard dose of 420 mg every 3 weeks, beginning on Day 2 of Cycle 1. Thereafter, both medications were administered on Day 1 of each 3-week cycle. Treatment continued for a minimum of 8 cycles and could be extended until disease progression, intolerable toxicity, or death.

Reporting group title	Pertuzumab +/- Trastuzumab (Cohort 3)

Reporting group description:

Females with HER2-positive metastatic breast cancer received single-agent treatment with pertuzumab. Recruitment for Cohort 3 was conducted following primary analysis of Cohorts 1 and 2. Pertuzumab was administered via IV infusion at a loading dose of 840 mg followed by a standard dose of 420 mg every 3 weeks, administered on Day 1 of each 3-week cycle. Participants with documented disease progression could have trastuzumab added to the regimen, per the dosing schedule described for Cohorts 1 and 2, to receive dual-agent treatment until disease progression, intolerable toxicity, or death.

Subject analysis set title	Pertuzumab (Cohort 3)
Subject analysis set type	Full analysis

Subject analysis set description:

Females with HER2-positive metastatic breast cancer received single-agent treatment with pertuzumab. Recruitment for Cohort 3 was conducted following primary analysis of Cohorts 1 and 2. Pertuzumab was administered via IV infusion at a loading dose of 840 mg followed by a standard dose of 420 mg every 3 weeks, administered on Day 1 of each 3-week cycle. The treatment regimen was maintained until disease progression, intolerable toxicity, death, and/or transition to dual-agent therapy with trastuzumab.

Primary: Cohorts 1 and 2: Percentage of Participants With a Confirmed Best Overall Response of Complete Response (CR) or Partial Response (PR) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 During Dual-Agent Treatment

End point title	Cohorts 1 and 2: Percentage of Participants With a Confirmed Best Overall Response of Complete Response (CR) or Partial Response (PR) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 During Dual-Agent Treatment[1][2]

End point description:

Tumor response was assessed using RECIST version 1.0 to determine the OR rate, or the percentage of participants with either confirmed CR or PR. CR was defined as the disappearance of all target lesions, and PR was defined as at least a 30 percent (%) decrease in the sum of the longest diameter compared to Baseline. Response was to be confirmed a minimum of 4 weeks after the initial response was documented. The OR rate was calculated as [number of participants meeting the above criteria divided by the number analyzed] multiplied by 100. All Treated Population: All randomized participants who received any amount of study medication (Cohorts 1 and 2 only).

End point type	Primary

End point timeframe:

Up to approximately 9.5 years (at Screening; on Day 15 of Cycles 2, 4, 6, and 8 [cycle length 3 weeks]; then every 3 months until disease progression)

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: Statistical significance was assessed using the lower bound of the 80% confidence interval for the OR rate. A clinically meaningful OR rate was defined as greater than or equal to (≥) 13% of participants. Providing the lower bound of the 80% confidence interval exceeded the critical value, the study was considered positive. No p-values were generated.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Values for Cohort 3 were reported as a separate, secondary endpoint.

End point values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage of participants				
number (confidence interval 80%)	24.2 (17.4 to 32.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Cohorts 1 and 2: Percentage of Participants With a Confirmed Best Overall Response of CR, PR, or Stable Disease (SD) According to RECIST Version 1.0 During Dual-Agent Treatment

End point title	Cohorts 1 and 2: Percentage of Participants With a Confirmed Best Overall Response of CR, PR, or Stable Disease (SD) According to RECIST Version 1.0 During Dual-Agent Treatment[3][4]

End point description:

Tumor response was assessed using RECIST version 1.0 to determine the CBR rate, or the percentage of participants with either confirmed CR or PR, or SD lasting at least 6 months. CR was defined as the disappearance of all target lesions, and PR was defined as at least a 30% decrease in the sum of the longest diameter compared to Baseline. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient (20%) increase to qualify for disease progression, in addition to no new target lesions. Response was to be confirmed a minimum of 4 weeks after the initial response was documented. The CBR rate was calculated as [number of participants meeting the above criteria divided by the number analyzed] multiplied by 100. All Treated Population (Cohorts 1 and 2).

End point type	Primary

End point timeframe:

Up to approximately 9.5 years (at Screening; on Day 15 of Cycles 2, 4, 6, and 8 [cycle length 3 weeks]; then every 3 months until disease progression)

Notes:

[3] - 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: Statistical significance was assessed using the lower bound of the 80% confidence interval for the CBR rate. A clinically meaningful CBR rate was defined as ≥25% of participants. Providing the lower bound of the 80% confidence interval exceeded the critical value, the study was considered positive. No p-values were generated.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Values for Cohort 3 were reported as a separate, secondary endpoint.

End point values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage of participants				
number (confidence interval 80%)	50 (41.5 to			

	58.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Duration of Response According to RECIST Version 1.0

End point title	Cohorts 1 and 2: Duration of Response According to RECIST Version 1.0[5]

End point description:

Tumor response was assessed using RECIST version 1.0 to determine OR and CBR rates. Duration of OR was defined as time from initial response of CR or PR to time of disease progression or death. Duration of CBR was defined similarly as time from initial response of CR or PR, or SD lasting at least 6 months, to time of disease progression or death. CR was defined as the disappearance of all target lesions, and PR was defined as at least a 30% decrease in the sum of the longest diameter compared to Baseline. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient (20%) increase to qualify for disease progression, in addition to no new target lesions. Participants without progression or death following confirmed CR or PR were censored at the last tumor assessment. Duration of response was estimated using Kaplan-Meier analysis and expressed in weeks. All Treated Population (Cohorts 1 and 2 only).

End point type	Secondary

End point timeframe:

Up to approximately 9.5 years (at Screening; on Day 15 of Cycles 2, 4, 6, and 8 [cycle length 3 weeks]; then every 3 months until disease progression)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis of Cohort 3 was exploratory and was therefore not reported.

End point values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: weeks				
median (full range (min-max))				
Objective response	40.1 (12 to 413)			
Clinical benefit response	50.14 (12.4 to 183.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Time to Objective Response According to RECIST Version 1.0

End point title	Cohorts 1 and 2: Time to Objective Response According to RECIST Version 1.0[6]

End point description:

Tumor response was assessed using RECIST version 1.0 to determine the OR rate. Time to response was defined as the time from first dose to the time of initial response of CR or PR. CR was defined as the disappearance of all target lesions, and PR was defined as at least a 30% decrease in the sum of the longest diameter compared to Baseline. Participants with disease progression were censored at the time of progression, and those with neither disease progression nor OR were censored at the last tumor assessment. Time to response was estimated using Kaplan-Meier analysis and expressed in weeks. All Treated Population (Cohorts 1 and 2 only).

End point type	Secondary

End point timeframe:

Up to approximately 21 months (at Screening; on Day 15 of Cycles 2, 4, 6, and 8 [cycle length 3 weeks]; then every 3 months until disease progression; final analysis using February 2008 cutoff date)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis of Cohort 3 was exploratory and was therefore not reported.

End point values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: weeks				
median (full range (min-max))	11.14 (4.9 to 37.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Percentage of Participants With Disease Progression According to RECIST Version 1.0

End point title	Cohorts 1 and 2: Percentage of Participants With Disease Progression According to RECIST Version 1.0[7]

End point description:

Tumor response was assessed using RECIST version 1.0 to assess for disease progression, defined as at least a 20% increase in the sum of the longest diameter, taking as reference the smallest sum of the longest diameter observed at previous tumor assessment, or the appearance of any new lesions. The percentage of participants with disease progression was calculated as [number of participants meeting the above criteria divided by the number analyzed] multiplied by 100. All Treated Population (Cohorts 1 and 2 only).

End point type	Secondary

End point timeframe:

Up to approximately 9.5 years (at Screening; on Day 15 of Cycles 2, 4, 6, and 8 [cycle length 3 weeks]; then every 3 months until disease progression)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis of Cohort 3 was exploratory and was therefore not reported.

End point values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage of participants				
number (not applicable)	93.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Time to Progression (TTP) According to RECIST Version 1.0

End point title	Cohorts 1 and 2: Time to Progression (TTP) According to RECIST Version 1.0[8]

End point description:

Tumor response was assessed using RECIST version 1.0 to assess for disease progression, defined as at least a 20% increase in the sum of the longest diameter, taking as reference the smallest sum of the longest diameter observed at previous tumor assessment, or the appearance of any new lesions. TTP was defined as the time from first dose to the time of first documented disease progression. Participants who withdrew from the study without documented progression were censored at the last tumor assessment. TTP was estimated using Kaplan-Meier analysis and expressed in weeks. All Treated Population (Cohorts 1 and 2 only).

End point type	Secondary

End point timeframe:

Up to approximately 9.5 years (at Screening; on Day 15 of Cycles 2, 4, 6, and 8 [cycle length 3 weeks]; then every 3 months until disease progression)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis of Cohort 3 was exploratory and was therefore not reported.

End point values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: weeks				
median (full range (min-max))	23.2 (4 to 244)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Progression-Free Survival (PFS) According to RECIST Version 1.0

End point title	Cohorts 1 and 2: Progression-Free Survival (PFS) According to RECIST Version 1.0[9]

End point description:

Tumor response was assessed using RECIST version 1.0 to assess for disease progression, defined as at least a 20% increase in the sum of the longest diameter, taking as reference the smallest sum of the longest diameter observed at previous tumor assessment, or the appearance of any new lesions. PFS was defined as the time from first dose to the time of disease progression or death. Participants without progression or death were censored at the last tumor assessment. PFS was estimated using Kaplan-Meier analysis and expressed in weeks. All Treated Population (Cohorts 1 and 2 only).

End point type	Secondary

End point timeframe:

Up to approximately 9.5 years (at Screening; on Day 15 of Cycles 2, 4, 6, and 8 [cycle length 3 weeks]; then every 3 months until disease progression)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis of Cohort 3 was exploratory and was therefore not reported.

End point values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: weeks				
median (confidence interval 80%)	24 (18 to 34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Percentage of Participants Who Died

End point title	Cohorts 1 and 2: Percentage of Participants Who Died[10]

End point description:

Participants were followed for survival data during and after treatment for a maximum of 3 years after the last dose until death, withdrawal of consent, or loss to follow-up. The percentage of participants who died was calculated as [number of participants with event divided by the number analyzed] multiplied by 100. All Treated Population (Cohorts 1 and 2 only).

End point type	Secondary

End point timeframe:

Up to approximately 4.5 years (during treatment; then every 4 months until death, withdrawn consent, loss to follow-up, or 3 years after last dose; final analysis using November 2010 cutoff date)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis of Cohort 3 was exploratory and was therefore not reported.

End point values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: percentage of participants				
number (not applicable)	30.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 1 and 2: Overall Survival (OS)

End point title	Cohorts 1 and 2: Overall Survival (OS)[11]

End point description:

Participants were followed for survival data during and after treatment for a maximum of 3 years after the last dose until death, withdrawal of consent, or loss to follow-up. OS was defined as the time from first dose to the time of death from any cause. Participants who did not experience death were censored at the last known alive date. OS was estimated using Kaplan-Meier and expressed in months. All Treated Population (Cohorts 1 and 2 only). 99999 = not estimable due to insufficient follow-up at the time the analysis was conducted.

End point type	Secondary

End point timeframe:

Up to approximately 4.5 years (during treatment; then every 4 months until death, withdrawn consent, loss to follow-up, or 3 years after last dose; final analysis using November 2010 cutoff date)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The analysis of Cohort 3 was exploratory and was therefore not reported.

End point values	Pertuzumab + Trastuzumab (Cohorts 1 and 2)			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: months				
median (confidence interval 80%)	38.5 (32 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 3: Percentage of Participants With a Confirmed Best Overall Response of CR or PR According to RECIST Version 1.0 During Single-Agent Treatment With Pertuzumab

End point title	Cohort 3: Percentage of Participants With a Confirmed Best Overall Response of CR or PR According to RECIST Version 1.0 During Single-Agent Treatment With Pertuzumab

End point description:

Tumor response was assessed using RECIST version 1.0 to determine the OR rate, or the percentage of participants with either confirmed CR or PR. CR was defined as the disappearance of all target lesions, and PR was defined as at least a 30% decrease in the sum of the longest diameter compared to Baseline. Response was to be confirmed a minimum of 4 weeks after the initial response was

documented. The OR rate was calculated as [number of participants meeting the above criteria divided by the number analyzed] multiplied by 100. All Treated Population (Cohort 3 only).

End point type	Secondary

End point timeframe:

Up to approximately 7.5 years (at Screening; on Day 15 of Cycles 2, 4, 6, and 8 [cycle length 3 weeks]; then every 3 months until disease progression)

End point values	Pertuzumab (Cohort 3)			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: percentage of participants				
number (confidence interval 80%)	3.4 (0.4 to 12.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 3: Percentage of Participants With a Confirmed Best Overall Response of CR, PR, or SD According to RECIST Version 1.0 During Single-Agent Treatment With Pertuzumab

End point title	Cohort 3: Percentage of Participants With a Confirmed Best Overall Response of CR, PR, or SD According to RECIST Version 1.0 During Single-Agent Treatment With Pertuzumab

End point description:

Tumor response was assessed using RECIST version 1.0 to determine the CBR rate, or the percentage of participants with either confirmed CR or PR, or SD lasting at least 6 months. CR was defined as the disappearance of all target lesions, and PR was defined as at least a 30% decrease in the sum of the longest diameter compared to Baseline. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient (20%) increase to qualify for disease progression, in addition to no new target lesions. Response was to be confirmed a minimum of 4 weeks after the initial response was documented. The CBR rate was calculated as [number of participants meeting the above criteria divided by the number analyzed] multiplied by 100. All Treated Population (Cohort 3 only).

End point type	Secondary

End point timeframe:

Up to approximately 7.5 years (at Screening; on Day 15 of Cycles 2, 4, 6, and 8 [cycle length 3 weeks]; then every 3 months until disease progression)

End point values	Pertuzumab (Cohort 3)			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: percentage of participants				
number (confidence interval 80%)	10.3 (3.9 to 21.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 9.5 years (from Day 1 until treatment discontinuation)

Adverse event reporting additional description:

Analysis Population Description: All Treated Population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Pertuzumab + Trastuzumab (Cohorts 1 and 2)

Reporting group description:

Females with HER2-positive metastatic breast cancer received dual-agent treatment with pertuzumab and trastuzumab. Recruitment for Cohorts 1 and 2 was conducted separately; however, the same regimen was administered to both sets of participants. Trastuzumab was administered via IV infusion as 2 mg/kg once weekly, or as 6 mg/kg every 3 weeks, beginning on Day 1 of Cycle 1. Pertuzumab was administered via IV infusion at a loading dose of 840 mg followed by a standard dose of 420 mg every 3 weeks, beginning on Day 2 of Cycle 1. Thereafter, both medications were administered on Day 1 of each 3-week cycle. Treatment continued for a minimum of 8 cycles and could be extended until disease progression, intolerable toxicity, or death.

Reporting group title	Pertuzumab +/- Trastuzumab (Cohort 3)

Reporting group description:

Females with HER2-positive metastatic breast cancer received single-agent treatment with pertuzumab. Recruitment for Cohort 3 was conducted following primary analysis of Cohorts 1 and 2. Pertuzumab was administered via IV infusion at a loading dose of 840 mg followed by a standard dose of 420 mg every 3 weeks, administered on Day 1 of each 3-week cycle. Participants with documented disease progression could have trastuzumab added to the regimen, per the dosing schedule described for Cohorts 1 and 2, to receive dual-agent treatment until disease progression, intolerable toxicity, or death.

Serious adverse events	Pertuzumab + Trastuzumab (Cohorts 1 and 2)	Pertuzumab +/- Trastuzumab (Cohort 3)	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 66 (18.18%)	1 / 29 (3.45%)	
number of deaths (all causes)	22	17	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 66 (0.00%)	1 / 29 (3.45%)	
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 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Toe amputation			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osmotic demyelination syndrome			
subjects affected / exposed	0 / 66 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (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			
Performance status decreased			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			

subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Paranoia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 66 (3.03%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			

subjects affected / exposed	1 / 66 (1.52%)	0 / 29 (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	1 / 66 (1.52%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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 (Cohorts 1 and 2)	Pertuzumab +/- Trastuzumab (Cohort 3)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 66 (93.94%)	28 / 29 (96.55%)	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 66 (0.00%)	4 / 29 (13.79%)	
occurrences (all)	0	5	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	1 / 66 (1.52%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 66 (22.73%)	4 / 29 (13.79%)	
occurrences (all)	18	5	
Dizziness			
subjects affected / exposed	9 / 66 (13.64%)	3 / 29 (10.34%)	
occurrences (all)	14	4	
Paraesthesia			
subjects affected / exposed	8 / 66 (12.12%)	0 / 29 (0.00%)	
occurrences (all)	9	0	
Hypoaesthesia			
subjects affected / exposed	4 / 66 (6.06%)	0 / 29 (0.00%)	
occurrences (all)	4	0	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	24 / 66 (36.36%)	8 / 29 (27.59%)	
occurrences (all)	35	11	
Asthenia			
subjects affected / exposed	9 / 66 (13.64%)	6 / 29 (20.69%)	
occurrences (all)	17	8	
Pyrexia			
subjects affected / exposed	6 / 66 (9.09%)	2 / 29 (6.90%)	
occurrences (all)	6	3	
Chest pain			
subjects affected / exposed	5 / 66 (7.58%)	2 / 29 (6.90%)	
occurrences (all)	5	2	
Chills			
subjects affected / exposed	4 / 66 (6.06%)	3 / 29 (10.34%)	
occurrences (all)	5	3	
Mucosal inflammation			
subjects affected / exposed	6 / 66 (9.09%)	1 / 29 (3.45%)	
occurrences (all)	6	1	
Influenza like illness			
subjects affected / exposed	3 / 66 (4.55%)	3 / 29 (10.34%)	
occurrences (all)	3	3	
Oedema peripheral			
subjects affected / exposed	5 / 66 (7.58%)	0 / 29 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	42 / 66 (63.64%)	16 / 29 (55.17%)	
occurrences (all)	106	28	
Toothache			
subjects affected / exposed	0 / 66 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	19 / 66 (28.79%)	12 / 29 (41.38%)	
occurrences (all)	35	18	
Vomiting			

subjects affected / exposed	9 / 66 (13.64%)	10 / 29 (34.48%)	
occurrences (all)	12	12	
Constipation			
subjects affected / exposed	9 / 66 (13.64%)	3 / 29 (10.34%)	
occurrences (all)	12	3	
Dyspepsia			
subjects affected / exposed	8 / 66 (12.12%)	2 / 29 (6.90%)	
occurrences (all)	9	2	
Abdominal pain upper			
subjects affected / exposed	5 / 66 (7.58%)	4 / 29 (13.79%)	
occurrences (all)	5	4	
Abdominal distension			
subjects affected / exposed	3 / 66 (4.55%)	3 / 29 (10.34%)	
occurrences (all)	3	4	
Abdominal pain			
subjects affected / exposed	4 / 66 (6.06%)	2 / 29 (6.90%)	
occurrences (all)	4	2	
Stomatitis			
subjects affected / exposed	6 / 66 (9.09%)	0 / 29 (0.00%)	
occurrences (all)	7	0	
Haemorrhoids			
subjects affected / exposed	4 / 66 (6.06%)	0 / 29 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 66 (18.18%)	4 / 29 (13.79%)	
occurrences (all)	18	6	
Dyspnoea			
subjects affected / exposed	6 / 66 (9.09%)	3 / 29 (10.34%)	
occurrences (all)	7	3	
Oropharyngeal pain			
subjects affected / exposed	3 / 66 (4.55%)	3 / 29 (10.34%)	
occurrences (all)	4	3	
Rhinorrhoea			

subjects affected / exposed	4 / 66 (6.06%)	0 / 29 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	18 / 66 (27.27%)	5 / 29 (17.24%)	
occurrences (all)	25	7	
Pruritus			
subjects affected / exposed	9 / 66 (13.64%)	4 / 29 (13.79%)	
occurrences (all)	10	7	
Nail disorder			
subjects affected / exposed	8 / 66 (12.12%)	2 / 29 (6.90%)	
occurrences (all)	8	2	
Dry skin			
subjects affected / exposed	5 / 66 (7.58%)	1 / 29 (3.45%)	
occurrences (all)	5	1	
Onychoclasis			
subjects affected / exposed	5 / 66 (7.58%)	0 / 29 (0.00%)	
occurrences (all)	6	0	
Rash pruritic			
subjects affected / exposed	4 / 66 (6.06%)	0 / 29 (0.00%)	
occurrences (all)	5	0	
Erythema			
subjects affected / exposed	1 / 66 (1.52%)	2 / 29 (6.90%)	
occurrences (all)	1	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 66 (6.06%)	1 / 29 (3.45%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 66 (18.18%)	4 / 29 (13.79%)	
occurrences (all)	14	4	
Myalgia			
subjects affected / exposed	12 / 66 (18.18%)	0 / 29 (0.00%)	
occurrences (all)	13	0	
Back pain			

subjects affected / exposed	4 / 66 (6.06%)	7 / 29 (24.14%)	
occurrences (all)	7	10	
Muscle spasms			
subjects affected / exposed	10 / 66 (15.15%)	1 / 29 (3.45%)	
occurrences (all)	15	1	
Pain in extremity			
subjects affected / exposed	6 / 66 (9.09%)	3 / 29 (10.34%)	
occurrences (all)	6	3	
Musculoskeletal chest pain			
subjects affected / exposed	5 / 66 (7.58%)	3 / 29 (10.34%)	
occurrences (all)	5	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 66 (12.12%)	1 / 29 (3.45%)	
occurrences (all)	11	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 66 (4.55%)	3 / 29 (10.34%)	
occurrences (all)	4	6	
Localised infection			
subjects affected / exposed	5 / 66 (7.58%)	0 / 29 (0.00%)	
occurrences (all)	6	0	
Rhinitis			
subjects affected / exposed	4 / 66 (6.06%)	1 / 29 (3.45%)	
occurrences (all)	5	1	
Urinary tract infection			
subjects affected / exposed	4 / 66 (6.06%)	1 / 29 (3.45%)	
occurrences (all)	6	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 66 (16.67%)	6 / 29 (20.69%)	
occurrences (all)	18	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2006	The protocol was updated to facilitate recruitment by expanding inclusion criteria, particularly to increase the permitted number of previous chemotherapy regimens and the amount of time lapsed since the last dose of trastuzumab. Changes were also made to HER2 testing methodology, the schedule of cardiac assessments, and the statistical analysis of early termination data.
31 July 2007	This protocol amendment added the recruitment of Cohort 3 in order to assess pertuzumab as a single agent. Specifications for treatment/dosing, assessments, statistical analyses, and follow-up were updated accordingly. The inclusion criteria were modified to stipulate that those enrolled into Cohort 3 must have received the last trastuzumab dose ≥4 weeks prior to Day 1.
19 June 2008	The protocol was amended to add OS as a secondary endpoint. To allow for collection of survival data, the end of study was defined as when all participants have either died, withdrawn consent, been lost to follow-up, or reached 3 years after the last dose of study medication. The dosing and schedule of assessments were further clarified for Cohort 3, particularly for those who progressed during single-agent therapy and for whom trastuzumab was introduced to the regimen.
24 June 2009	Significant updates to the protocol included the definition of postmenopausal women, contraceptive requirements, and procedures in the event of a pregnancy. Further, the analysis of efficacy assessments in Cohort 3 was specified to occur after all participants had reached at least 8 cycles of treatment.
18 January 2012	The protocol amendment included reduction and simplification of study-related procedures and assessments for participants currently on study treatment since the primary objective of the study had, at the time, already been completed.
07 April 2015	The end of the study was initially defined to occur once all participants in all cohorts had died, withdrawn consent, been lost to follow-up, or reached 3 years after last dose of study drug. However, the protocol was amended to specify the Sponsor's intent to terminate the study while ensuring that the last remaining participant on study treatment could continue to receive treatment for as long as he/she needed and as long as adverse events were properly managed and reported.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although the study was designed as single-arm study, as reflected in the study title, an additional cohort was opened to evaluate the efficacy and safety of single-agent pertuzumab.

Notes: