Clinical trial results:
A Multicenter, Open-Label, Single-Arm Study of Pertuzumab in Combination with Trastuzumab and a Taxane in First Line Treatment of Patients with HER2-Positive Advanced (Metastatic or Locally Recurrent) Breast Cancer

Summary

EudraCT number	2011-005334-20
Trial protocol	AT FI FR ES SI GB NL DE BE HU PT GR SE IT EE LT PL
Global end of trial date	20 September 2019

Results information

Result version number	v1 (current)
This version publication date	16 September 2020
First version publication date	16 September 2020

Trial information

Trial identification

Sponsor protocol code	MO28047

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01572038
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2019
Global end of trial reached?	Yes
Global end of trial date	20 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study was to evaluate the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane.

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. All participants were required to read and sign an informed consent form.

Background therapy:

Trastuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 8 mg/kg, followed by 6 mg/kg on Day 1 or Day 2 of each subsequent 3-weekly cycle; in line with approved local Product Information and/or recognized clinical practice guidelines. Commercial Herceptin (trastuzumab) was obtained directly by the site for intravenous use during this study. A taxane (docetaxel or paclitaxel or nab-paclitaxel) was administered in line with the respective Product Information and/or recognized clinical practice guidelines. The taxane could have been administered before or after the monoclonal antibody (pertuzumab and trastuzumab) infusions. Commercial docetaxel and/or paclitaxel and nab-paclitaxel was obtained locally by the investigational sites.

Evidence for comparator: -

Actual start date of recruitment	01 June 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Algeria: 29
Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Brazil: 44
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	China: 52
Country: Number of subjects enrolled	Ecuador: 4
Country: Number of subjects enrolled	Egypt: 26
Country: Number of subjects enrolled	Estonia: 3

Country: Number of subjects enrolled	Finland: 15
Country: Number of subjects enrolled	France: 185
Country: Number of subjects enrolled	Germany: 82
Country: Number of subjects enrolled	Greece: 40
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Israel: 49
Country: Number of subjects enrolled	Italy: 115
Country: Number of subjects enrolled	Lebanon: 8
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Mexico: 46
Country: Number of subjects enrolled	Morocco: 16
Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Pakistan: 17
Country: Number of subjects enrolled	Peru: 11
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Portugal: 24
Country: Number of subjects enrolled	Saudi Arabia: 11
Country: Number of subjects enrolled	Serbia: 15
Country: Number of subjects enrolled	Slovenia: 8
Country: Number of subjects enrolled	Spain: 168
Country: Number of subjects enrolled	Sweden: 25
Country: Number of subjects enrolled	Turkey: 30
Country: Number of subjects enrolled	Ukraine: 35
Country: Number of subjects enrolled	United Arab Emirates: 5
Country: Number of subjects enrolled	United Kingdom: 142
Country: Number of subjects enrolled	Uruguay: 6
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 5
Worldwide total number of subjects	1436
EEA total number of subjects	959

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)	1124
From 65 to 84 years	310
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1697 patients were screened: 261 failed screening and 1436 were enrolled in the study.

Period 1

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

Arms

Arm title	Pertuzumab + Trastuzumab + Taxane

Arm description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4358451
Other name	Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 or Day 2 of each subsequent 3 weekly cycle.

Number of subjects in period 1	Pertuzumab + Trastuzumab + Taxane
Started	1436
Received at Least One Dose of Study Drug	1436
Completed	445
Not completed	991
Enrolled into Another Trial	3
Participated in Another Trial	3
Termination by Sponsor	2
Consent withdrawn by subject	204
Physician decision	20
Patient Decision	14
Death	648
Progressive Disease	8

Site Closed Before Completing Form	6
Sponsor Decision	1
Lost to follow-up	81
Patient Deterioration	1

Baseline characteristics

Reporting groups	
Reporting group title	Pertuzumab + Trastuzumab + Taxane
Reporting group description:	
Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.	

Reporting group values	Pertuzumab + Trastuzumab + Taxane	Total	
Number of subjects	1436	1436	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1124	1124	
From 65-84 years	310	310	
85 years and over	2	2	
Age Continuous Units: Years			
arithmetic mean	54.4		
standard deviation	± 12.10	-	
Sex: Female, Male Units: Participants			
Female	1429	1429	
Male	7	7	
Age Categorical (≤65 or >65 Years Old) Units: Subjects			
≤65 Years Old	1167	1167	
>65 Years Old	269	269	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	1032	1032	
Black	9	9	
Asian	88	88	
Native American	28	28	
Other	57	57	
Not Applicable as per Local Regulations	222	222	
Ethnicity Units: Subjects			
Hispanic/Latino	269	269	

Chinese	57	57	
Japanese	2	2	
Mixed Ethnicity	18	18	
Indian	21	21	
Other	495	495	
Not Applicable as per Local Regulations	574	574	
Geographic Region of Enrollment			
Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.			
Units: Subjects			
Europe	1009	1009	
Asia	177	177	
North America	34	34	
South America	121	121	
Africa	71	71	
Other (Australia)	24	24	
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
Grade 0 or 1	1371	1371	
Grade 2	63	63	
Missing	2	2	
Visceral Disease at Baseline			
The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.			
Units: Subjects			
Visceral Disease	992	992	
Non-visceral Disease	444	444	
Hormone Receptor Status of Disease at Baseline			
Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.			
Units: Subjects			
Positive	918	918	
Negative	512	512	
Unknown	6	6	
Prior Neoadjuvant or Adjuvant Chemotherapy Received Units: Subjects			
Prior (Neo)Adjuvant Chemotherapy	786	786	
No Prior (Neo)Adjuvant Chemotherapy	650	650	
Previous Trastuzumab Therapy Received for Breast Cancer			

Units: Subjects			
Previous Trastuzumab Therapy	400	400	
No Previous Trastuzumab Therapy	1036	1036	
Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel Units: Subjects			
Docetaxel	775	775	
Paclitaxel	588	588	
Nab-Paclitaxel	65	65	
None	8	8	
Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline Units: Subjects			
Measurable Disease	1198	1198	
Non-Measurable Disease	238	238	

Subject analysis sets

Subject analysis set title	Europe
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Asia
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	North America
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	South America
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Africa
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Other (Australia)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Age ≤65 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Age >65 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Docetaxel
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received docetaxel as their taxane chemotherapy, per the investigator's choice.

Subject analysis set title	Paclitaxel
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received paclitaxel as their taxane chemotherapy, per the investigator's choice.

Subject analysis set title	Nab-Paclitaxel
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received nab-paclitaxel as their taxane chemotherapy, per the investigator's choice.

Subject analysis set title	ECOG Performance Status 0 or 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	ECOG Performance Status 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Visceral Disease
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of

consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Non-Visceral Disease
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Prior (Neo)Adjuvant Chemotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	No Prior (Neo)Adjuvant Chemotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Hormone Receptor Positive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Hormone Receptor Negative
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Hormone Receptor Status Unknown
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Previous Trastuzumab Therapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	No Previous Trastuzumab Therapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Reporting group values	Europe	Asia	North America
Number of subjects	1009	177	34
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous Units: Years			
arithmetic mean	55.4	50.8	56.3
standard deviation	± 12.14	± 11.75	± 11.32
Sex: Female, Male Units: Participants			
Female			
Male			
Age Categorical (≤65 or >65 Years Old) Units: Subjects			
≤65 Years Old			
>65 Years Old			
Race/Ethnicity, Customized Units: Subjects			
Caucasian			
Black			
Asian			
Native American			
Other			
Not Applicable as per Local Regulations			
Ethnicity Units: Subjects			
Hispanic/Latino			
Chinese			
Japanese			
Mixed Ethnicity			
Indian			
Other			
Not Applicable as per Local Regulations			
Geographic Region of Enrollment			
Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.			
Units: Subjects			

Europe Asia North America South America Africa Other (Australia)			
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
Grade 0 or 1 Grade 2 Missing			
Visceral Disease at Baseline			
The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.			
Units: Subjects			
Visceral Disease Non-visceral Disease			
Hormone Receptor Status of Disease at Baseline			
Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.			
Units: Subjects			
Positive Negative Unknown			
Prior Neoadjuvant or Adjuvant Chemotherapy Received Units: Subjects			
Prior (Neo)Adjuvant Chemotherapy No Prior (Neo)Adjuvant Chemotherapy			
Previous Trastuzumab Therapy Received for Breast Cancer Units: Subjects			
Previous Trastuzumab Therapy No Previous Trastuzumab Therapy			
Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel Units: Subjects			
Docetaxel Paclitaxel Nab-Paclitaxel None			
Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline Units: Subjects			

Measurable Disease			
Non-Measurable Disease			

Reporting group values	South America	Africa	Other (Australia)
Number of subjects	121	71	24
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: Years			
arithmetic mean	54.5	48.0	53.8
standard deviation	± 11.53	± 10.55	± 11.49
Sex: Female, Male			
Units: Participants			
Female			
Male			
Age Categorical (≤65 or >65 Years Old)			
Units: Subjects			
≤65 Years Old			
>65 Years Old			
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian			
Black			
Asian			
Native American			
Other			
Not Applicable as per Local Regulations			
Ethnicity			
Units: Subjects			
Hispanic/Latino			
Chinese			
Japanese			
Mixed Ethnicity			
Indian			
Other			
Not Applicable as per Local Regulations			
Geographic Region of Enrollment			
Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia,			

Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.			
Units: Subjects			
Europe Asia North America South America Africa Other (Australia)			
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
Grade 0 or 1 Grade 2 Missing			
Visceral Disease at Baseline			
The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.			
Units: Subjects			
Visceral Disease Non-visceral Disease			
Hormone Receptor Status of Disease at Baseline			
Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.			
Units: Subjects			
Positive Negative Unknown			
Prior Neoadjuvant or Adjuvant Chemotherapy Received Units: Subjects			
Prior (Neo)Adjuvant Chemotherapy No Prior (Neo)Adjuvant Chemotherapy			
Previous Trastuzumab Therapy Received for Breast Cancer Units: Subjects			
Previous Trastuzumab Therapy No Previous Trastuzumab Therapy			
Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel Units: Subjects			
Docetaxel Paclitaxel Nab-Paclitaxel			

None			
Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline Units: Subjects			
Measurable Disease			
Non-Measurable Disease			

Reporting group values	Age ≤65 Years	Age >65 Years	Docetaxel
Number of subjects	1167	269	775
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous Units: Years			
arithmetic mean	50.3	72.0	52.9
standard deviation	± 9.30	± 4.68	± 11.77
Sex: Female, Male Units: Participants			
Female			
Male			
Age Categorical (≤65 or >65 Years Old) Units: Subjects			
≤65 Years Old			
>65 Years Old			
Race/Ethnicity, Customized Units: Subjects			
Caucasian			
Black			
Asian			
Native American			
Other			
Not Applicable as per Local Regulations			
Ethnicity Units: Subjects			
Hispanic/Latino			
Chinese			
Japanese			
Mixed Ethnicity			
Indian			
Other			
Not Applicable as per Local Regulations			

Geographic Region of Enrollment			
Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.			
Units: Subjects			
Europe Asia North America South America Africa Other (Australia)			
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
Grade 0 or 1 Grade 2 Missing			
Visceral Disease at Baseline			
The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.			
Units: Subjects			
Visceral Disease Non-visceral Disease			
Hormone Receptor Status of Disease at Baseline			
Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.			
Units: Subjects			
Positive Negative Unknown			
Prior Neoadjuvant or Adjuvant Chemotherapy Received Units: Subjects			
Prior (Neo)Adjuvant Chemotherapy No Prior (Neo)Adjuvant Chemotherapy			
Previous Trastuzumab Therapy Received for Breast Cancer Units: Subjects			
Previous Trastuzumab Therapy No Previous Trastuzumab Therapy			
Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel Units: Subjects			

Docetaxel Paclitaxel Nab-Paclitaxel None			
Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline Units: Subjects			
Measurable Disease Non-Measurable Disease			

Reporting group values	Paclitaxel	Nab-Paclitaxel	ECOG Performance Status 0 or 1
Number of subjects	588	65	1371
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	56.3	54.1	54.2
standard deviation	± 12.21	± 12.53	± 12.00
Sex: Female, Male Units: Participants			
Female Male			
Age Categorical (≤65 or >65 Years Old) Units: Subjects			
≤65 Years Old >65 Years Old			
Race/Ethnicity, Customized Units: Subjects			
Caucasian Black Asian Native American Other Not Applicable as per Local Regulations			
Ethnicity Units: Subjects			
Hispanic/Latino Chinese Japanese Mixed Ethnicity			

Indian Other Not Applicable as per Local Regulations			
Geographic Region of Enrollment			
Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.			
Units: Subjects			
Europe Asia North America South America Africa Other (Australia)			
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
Grade 0 or 1 Grade 2 Missing			
Visceral Disease at Baseline			
The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.			
Units: Subjects			
Visceral Disease Non-visceral Disease			
Hormone Receptor Status of Disease at Baseline			
Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.			
Units: Subjects			
Positive Negative Unknown			
Prior Neoadjuvant or Adjuvant Chemotherapy Received Units: Subjects			
Prior (Neo)Adjuvant Chemotherapy No Prior (Neo)Adjuvant Chemotherapy			
Previous Trastuzumab Therapy Received for Breast Cancer Units: Subjects			
Previous Trastuzumab Therapy No Previous Trastuzumab Therapy			

Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel Units: Subjects			
Docetaxel Paclitaxel Nab-Paclitaxel None			
Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline Units: Subjects			
Measurable Disease Non-Measurable Disease			

Reporting group values	ECOG Performance Status 2	Visceral Disease	Non-Visceral Disease
Number of subjects	63	992	444
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	58.1	54.6	53.8
standard deviation	± 13.81	± 12.05	± 12.21
Sex: Female, Male Units: Participants			
Female Male			
Age Categorical (≤65 or >65 Years Old) Units: Subjects			
≤65 Years Old >65 Years Old			
Race/Ethnicity, Customized Units: Subjects			
Caucasian Black Asian Native American Other Not Applicable as per Local Regulations			
Ethnicity Units: Subjects			
Hispanic/Latino			

Chinese Japanese Mixed Ethnicity Indian Other Not Applicable as per Local Regulations			
Geographic Region of Enrollment			
Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.			
Units: Subjects			
Europe Asia North America South America Africa Other (Australia)			
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
Grade 0 or 1 Grade 2 Missing			
Visceral Disease at Baseline			
The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.			
Units: Subjects			
Visceral Disease Non-visceral Disease			
Hormone Receptor Status of Disease at Baseline			
Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.			
Units: Subjects			
Positive Negative Unknown			
Prior Neoadjuvant or Adjuvant Chemotherapy Received Units: Subjects			
Prior (Neo)Adjuvant Chemotherapy No Prior (Neo)Adjuvant Chemotherapy			
Previous Trastuzumab Therapy Received for Breast Cancer			

Units: Subjects			
Previous Trastuzumab Therapy			
No Previous Trastuzumab Therapy			
Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel			
Units: Subjects			
Docetaxel			
Paclitaxel			
Nab-Paclitaxel			
None			
Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline			
Units: Subjects			
Measurable Disease			
Non-Measurable Disease			

Reporting group values	Prior (Neo)Adjuvant Chemotherapy	No Prior (Neo)Adjuvant Chemotherapy	Hormone Receptor Positive
Number of subjects	786	650	918
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: Years			
arithmetic mean	54.6	54.0	54.1
standard deviation	± 11.79	± 12.46	± 12.07
Sex: Female, Male			
Units: Participants			
Female			
Male			
Age Categorical (≤65 or >65 Years Old)			
Units: Subjects			
≤65 Years Old			
>65 Years Old			
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian			
Black			
Asian			
Native American			
Other			

Not Applicable as per Local Regulations			
Ethnicity Units: Subjects			
Hispanic/Latino Chinese Japanese Mixed Ethnicity Indian Other Not Applicable as per Local Regulations			
Geographic Region of Enrollment			
Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.			
Units: Subjects			
Europe Asia North America South America Africa Other (Australia)			
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
Grade 0 or 1 Grade 2 Missing			
Visceral Disease at Baseline			
The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.			
Units: Subjects			
Visceral Disease Non-visceral Disease			
Hormone Receptor Status of Disease at Baseline			
Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.			
Units: Subjects			
Positive Negative Unknown			
Prior Neoadjuvant or Adjuvant Chemotherapy Received Units: Subjects			

Prior (Neo)Adjuvant Chemotherapy			
No Prior (Neo)Adjuvant Chemotherapy			
Previous Trastuzumab Therapy Received for Breast Cancer			
Units: Subjects			
Previous Trastuzumab Therapy			
No Previous Trastuzumab Therapy			
Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel			
Units: Subjects			
Docetaxel			
Paclitaxel			
Nab-Paclitaxel			
None			
Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline			
Units: Subjects			
Measurable Disease			
Non-Measurable Disease			

Reporting group values	Hormone Receptor Negative	Hormone Receptor Status Unknown	Previous Trastuzumab Therapy
Number of subjects	512	6	400
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: Years			
arithmetic mean	54.9	46.7	52.8
standard deviation	± 12.17	± 7.31	± 11.80
Sex: Female, Male			
Units: Participants			
Female			
Male			
Age Categorical (≤65 or >65 Years Old)			
Units: Subjects			
≤65 Years Old			
>65 Years Old			
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian			

Black Asian Native American Other Not Applicable as per Local Regulations			
Ethnicity Units: Subjects			
Hispanic/Latino Chinese Japanese Mixed Ethnicity Indian Other Not Applicable as per Local Regulations			
Geographic Region of Enrollment			
Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.			
Units: Subjects			
Europe Asia North America South America Africa Other (Australia)			
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
Grade 0 or 1 Grade 2 Missing			
Visceral Disease at Baseline			
The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.			
Units: Subjects			
Visceral Disease Non-visceral Disease			
Hormone Receptor Status of Disease at Baseline			
Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.			
Units: Subjects			
Positive Negative			

Unknown			
Prior Neoadjuvant or Adjuvant Chemotherapy Received Units: Subjects			
Prior (Neo)Adjuvant Chemotherapy			
No Prior (Neo)Adjuvant Chemotherapy			
Previous Trastuzumab Therapy Received for Breast Cancer Units: Subjects			
Previous Trastuzumab Therapy			
No Previous Trastuzumab Therapy			
Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel Units: Subjects			
Docetaxel			
Paclitaxel			
Nab-Paclitaxel			
None			
Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline Units: Subjects			
Measurable Disease			
Non-Measurable Disease			

Reporting group values	No Previous Trastuzumab Therapy		
Number of subjects	1036		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous Units: Years			
arithmetic mean	55.0		
standard deviation	± 12.16		
Sex: Female, Male Units: Participants			
Female			
Male			
Age Categorical (≤65 or >65 Years Old) Units: Subjects			
≤65 Years Old			
>65 Years Old			

Race/Ethnicity, Customized Units: Subjects			
Caucasian Black Asian Native American Other Not Applicable as per Local Regulations			
Ethnicity Units: Subjects			
Hispanic/Latino Chinese Japanese Mixed Ethnicity Indian Other Not Applicable as per Local Regulations			
Geographic Region of Enrollment			
Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.			
Units: Subjects			
Europe Asia North America South America Africa Other (Australia)			
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.			
Units: Subjects			
Grade 0 or 1 Grade 2 Missing			
Visceral Disease at Baseline			
The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.			
Units: Subjects			
Visceral Disease Non-visceral Disease			
Hormone Receptor Status of Disease at Baseline			
Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.			

Units: Subjects			
Positive Negative Unknown			
Prior Neoadjuvant or Adjuvant Chemotherapy Received Units: Subjects			
Prior (Neo)Adjuvant Chemotherapy No Prior (Neo)Adjuvant Chemotherapy			
Previous Trastuzumab Therapy Received for Breast Cancer Units: Subjects			
Previous Trastuzumab Therapy No Previous Trastuzumab Therapy			
Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel Units: Subjects			
Docetaxel Paclitaxel Nab-Paclitaxel None			
Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline Units: Subjects			
Measurable Disease Non-Measurable Disease			

End points reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Taxane

Reporting group description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Europe
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Asia
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	North America
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	South America
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Africa
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Other (Australia)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Age ≤65 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel,

paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Age >65 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Docetaxel
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received docetaxel as their taxane chemotherapy, per the investigator's choice.

Subject analysis set title	Paclitaxel
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received paclitaxel as their taxane chemotherapy, per the investigator's choice.

Subject analysis set title	Nab-Paclitaxel
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received nab-paclitaxel as their taxane chemotherapy, per the investigator's choice.

Subject analysis set title	ECOG Performance Status 0 or 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	ECOG Performance Status 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Visceral Disease
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Non-Visceral Disease
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Prior (Neo)Adjuvant Chemotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	No Prior (Neo)Adjuvant Chemotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Hormone Receptor Positive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Hormone Receptor Negative
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Hormone Receptor Status Unknown
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	Previous Trastuzumab Therapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Subject analysis set title	No Previous Trastuzumab Therapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Primary: Overview of the Number of Participants with at Least One Treatment-Emergent Adverse Event, Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0)

End point title	Overview of the Number of Participants with at Least One Treatment-Emergent Adverse Event, Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0)[1]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed

as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade ≥3, pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent. TEAEs of special interest included LVEF decreased, liver enzymes increased, and suspected transmission of infectious agent by the study drug.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Any TEAE - Any Grade	1419			
Any TEAE - Grade 3 or Higher (≥3)	879			
Any Serious TEAE	535			
Any TEAE Leading to Death	31			
Any TEAE Related to Pertuzumab - Any Grade	1037			
Any TEAE Related to Trastuzumab - Any Grade	946			
Any TEAE Related to Taxane - Any Grade	1342			
Any TEAE Related to Pertuzumab - Grade ≥3	286			
Any TEAE Related to Trastuzumab - Grade ≥3	245			
Any TEAE Related to Taxane - Grade ≥3	514			
Any TEAE Leading to Interruption of Pertuzumab	334			
Any TEAE Leading to Interruption of Trastuzumab	386			
Any TEAE Leading to Interruption of Taxane	354			
Any TEAE Leading to Discontinuation of Pertuzumab	140			
Any TEAE Leading to Discontinuation of Trastuzumab	133			
Any TEAE Leading to Discontinuation of Taxane	286			
Any TEAE to Monitor - Any Grade	1320			
Any TEAE to Monitor - Grade ≥3	535			
Any TEAE of Special Interest	91			
Any TEAE Within 28 Days of Treatmt Discontinuation	975			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Died Over the Course of the Study by Reported Cause of Death (Adverse Events Leading to Death by System Organ Class and Preferred Term)

End point title	Number of Participants Who Died Over the Course of the Study by Reported Cause of Death (Adverse Events Leading to Death by System Organ Class and Preferred Term)[2]

End point description:

All adverse events leading to death, regardless of whether they were classified as treatment emergent, are listed by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities, version 22.1 (MedDRA version 22.1); PTs that are part of a given SOC are listed in the rows directly below each SOC within the results table. Admin. = administration; Mediast. = mediastinal

End point type	Primary

End point timeframe:

The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

Notes:

[2] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Total Number of Deaths	658			
Number of Deaths by Cause: Progressive Disease	581			
Number of Deaths by Cause: Other	42			
Number of Deaths by Cause: Adverse Event (Total)	35			
Infections and Infestations (SOC)	11			
Peritonitis (PT)	1			
Pneumonia (PT)	5			
Respiratory Tract Infection (PT)	1			
Sepsis (PT)	3			
Septic Shock (PT)	1			
Cardiac Disorders (SOC)	7			
Cardiac Arrest (PT)	2			
Cardiac Failure (PT)	1			
Cardiac Failure Congestive (PT)	1			
Cardio-respiratory Arrest (PT)	1			
Myocardial Infarction (PT)	1			

Right Ventricular Failure (PT)	1			
General Disorders & Admin. Site Conditions (SOC)	6			
Death (PT)	6			
Blood and Lymphatic System Disorders (SOC)	3			
Febrile Neutropenia (PT)	1			
Neutropenia (PT)	1			
Thrombocytopenia (PT)	1			
Respiratory, Thoracic & Mediast. Disorders (SOC)	3			
Acute Respiratory Distress Syndrome (PT)	1			
Aspiration (PT)	1			
Pneumonitis (PT)	1			
Gastrointestinal Disorders (SOC)	2			
Pancreatitis (PT)	1			
Pancreatitis Chronic (PT)	1			
Nervous System Disorders (SOC)	2			
Hepatic Encephalopathy (PT)	1			
Ischemic Stroke (PT)	1			
Metabolism and Nutrition Disorders (SOC)	1			
Hypoglycaemia (PT)	1			
Hepatobiliary Disorders (SOC)	1			
Hepatic Failure (PT)	1			
Psychiatric Disorders (SOC)	1			
Delirium (PT)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Died Within 6 Months of Starting Study Treatment by Reported Cause of Death (Adverse Events Leading to Death by System Organ Class and Preferred Term)

End point title	Number of Participants Who Died Within 6 Months of Starting Study Treatment by Reported Cause of Death (Adverse Events Leading to Death by System Organ Class and Preferred Term)[3]

End point description:

All adverse events leading to death, regardless of whether they were classified as treatment emergent, are listed by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities, version 22.1 (MedDRA version 22.1); PTs that are part of a given SOC are listed in the rows directly below each SOC within the results table. Admin. = administration; Mediast. = mediastinal

End point type	Primary

End point timeframe:

The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Total Number of Deaths	38			
Number of Deaths by Cause: Progressive Disease	18			
Number of Deaths by Cause: Other	1			
Number of Deaths by Cause: Adverse Event (Total)	19			
Infections and Infestations (SOC)	6			
Peritonitis (PT)	1			
Pneumonia (PT)	2			
Respiratory Tract Infection (PT)	1			
Sepsis (PT)	2			
General Disorders & Admin. Site Conditions (SOC)	4			
Death (PT)	4			
Blood and Lymphatic System Disorders (SOC)	3			
Febrile Neutropenia (PT)	1			
Neutropenia (PT)	1			
Thrombocytopenia (PT)	1			
Cardiac Disorders (SOC)	2			
Cardiac Arrest (PT)	1			
Cardio-Respiratory Arrest (PT)	1			
Respiratory, Thoracic & Mediast. Disorders (SOC)	2			
Acute Respiratory Distress Syndrome (PT)	1			
Pneumonitis (PT)	1			
Gastrointestinal Disorders (SOC)	1			
Pancreatitis (PT)	1			
Nervous System Disorders (SOC)	1			
Hepatic Encephalopathy (PT)	1			
Metabolism and Nutrition Disorders (SOC)	1			
Hypoglycaemia (PT)	1			
Hepatobiliary Disorders (SOC)	1			
Hepatic Failure (PT)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Grade ≥3 Treatment-Emergent Adverse Events, Occurring in ≥1% of Participants by System Organ Class and Preferred Term

End point title	Number of Participants with Grade ≥3 Treatment-Emergent Adverse Events, Occurring in ≥1% of Participants by System Organ Class and Preferred Term[4]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was used to code AEs by system organ class (SOC) and preferred term (PT); PTs that are part of a given SOC are listed in the rows directly below each SOC within the results table. If a participant experienced the same AE at more than one severity grade, only the most severe grade was presented.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Any TEAE - Grade (Gr.) 3	676			
Any TEAE - Gr. 4	172			
Any TEAE - Gr. 5	31			
Gastrointestinal Disorders (SOC) - Gr. 3	163			
Gastrointestinal Disorders (SOC) - Gr. 4	4			
Gastrointestinal Disorders (SOC) - Gr. 5	2			
Diarrhoea (PT) - Gr. 3	119			
Diarrhoea (PT) - Gr. 4	1			
Diarrhoea (PT) - Gr. 5	0			
Vomiting (PT) - Gr. 3	19			
Vomiting (PT) - Gr. 4	0			
Vomiting (PT) - Gr. 5	0			
Skin & Subcutaneous Tissue Disorders (SOC) - Gr. 3	56			
Skin & Subcutaneous Tissue Disorders (SOC) - Gr. 4	0			
Skin & Subcutaneous Tissue Disorders (SOC) - Gr. 5	0			
Gen. Disorders & Admin.Site Conditions (SOC)-Gr. 3	100			
Gen. Disorders & Admin.Site Conditions (SOC)-Gr. 4	0			
Gen. Disorders & Admin.Site Conditions (SOC)-Gr. 5	3			
Fatigue (PT) - Gr. 3	36			
Fatigue (PT) - Gr. 4	0			
Fatigue (PT) - Gr. 5	0			
Asthenia (PT) - Gr. 3	29			
Asthenia (PT) - Gr. 4	0			
Asthenia (PT) - Gr. 5	0			
Mucosal Inflammation (PT) - Gr. 3	14			

Mucosal Inflammation (PT) - Gr. 4	0			
Mucosal Inflammation (PT) - Gr. 5	0			
Nervous System Disorders (SOC) - Gr. 3	139			
Nervous System Disorders (SOC) - Gr. 4	0			
Nervous System Disorders (SOC) - Gr. 5	2			
Neuropathy Peripheral (PT) - Gr. 3	26			
Neuropathy Peripheral (PT) - Gr. 4	0			
Neuropathy Peripheral (PT) - Gr. 5	0			
Syncope (PT) - Gr. 3	24			
Syncope (PT) - Gr. 4	0			
Syncope (PT) - Gr. 5	0			
Headache (PT) - Gr. 3	17			
Headache (PT) - Gr. 4	0			
Headache (PT) - Gr. 5	0			
Paraesthesia (PT) - Gr. 3	14			
Paraesthesia (PT) - Gr. 4	0			
Paraesthesia (PT) - Gr. 5	0			
Peripheral Sensory Neuropathy (PT) - Gr. 3	14			
Peripheral Sensory Neuropathy (PT) - Gr. 4	0			
Peripheral Sensory Neuropathy (PT) - Gr. 5	0			
Infections and Infestations (SOC) - Gr. 3	148			
Infections and Infestations (SOC) - Gr. 4	19			
Infections and Infestations (SOC) - Gr. 5	10			
Pneumonia (PT) - Gr. 3	22			
Pneumonia (PT) - Gr. 4	1			
Pneumonia (PT) - Gr. 5	4			
Vascular Device Infection (PT) - Gr. 3	14			
Vascular Device Infection (PT) - Gr. 4	0			
Vascular Device Infection (PT) - Gr. 5	0			
Device Related Infection (PT) - Gr. 3	14			
Device Related Infection (PT) - Gr. 4	0			
Device Related Infection (PT) - Gr. 5	0			
Musculo. & Connective Tissue Disorders (SOC)-Gr. 3	75			
Musculo. & Connective Tissue Disorders (SOC)-Gr. 4	0			
Musculo. & Connective Tissue Disorders (SOC)-Gr. 5	0			
Resp., Thoracic & Mediast. Disorders (SOC) - Gr. 3	62			
Resp., Thoracic & Mediast. Disorders (SOC) - Gr. 4	5			
Resp., Thoracic & Mediast. Disorders (SOC) - Gr. 5	3			
Pulmonary Embolism (PT) - Gr. 3	21			
Pulmonary Embolism (PT) - Gr. 4	2			
Pulmonary Embolism (PT) - Gr. 5	0			
Dyspnoea (PT) - Gr. 3	19			
Dyspnoea (PT) - Gr. 4	1			
Dyspnoea (PT) - Gr. 5	0			

Blood & Lymphatic System Disorders (SOC) - Gr. 3	158			
Blood & Lymphatic System Disorders (SOC) - Gr. 4	104			
Blood & Lymphatic System Disorders (SOC) - Gr. 5	3			
Neutropenia (PT) - Gr. 3	77			
Neutropenia (PT) - Gr. 4	67			
Neutropenia (PT) - Gr. 5	1			
Febrile Neutropenia (PT) - Gr. 3	51			
Febrile Neutropenia (PT) - Gr. 4	38			
Febrile Neutropenia (PT) - Gr. 5	1			
Anaemia (PT) - Gr. 3	29			
Anaemia (PT) - Gr. 4	0			
Anaemia (PT) - Gr. 5	0			
Leukopenia (PT) - Gr. 3	15			
Leukopenia (PT) - Gr. 4	3			
Leukopenia (PT) - Gr. 5	0			
Investigations (SOC) - Gr. 3	116			
Investigations (SOC) - Gr. 4	20			
Investigations (SOC) - Gr. 5	0			
Neutrophil Count Decreased (PT) - Gr. 3	25			
Neutrophil Count Decreased (PT) - Gr. 4	13			
Neutrophil Count Decreased (PT) - Gr. 5	0			
Ejection Fraction Decreased (PT) - Gr. 3	22			
Ejection Fraction Decreased (PT) - Gr. 4	2			
Ejection Fraction Decreased (PT) - Gr. 5	0			
Gamma-Glutamyltransferase Increased (PT) - Gr. 3	19			
Gamma-Glutamyltransferase Increased (PT) - Gr. 4	1			
Gamma-Glutamyltransferase Increased (PT) - Gr. 5	0			
White Blood Cell Count Decreased (PT) - Gr. 3	16			
White Blood Cell Count Decreased (PT) - Gr. 4	2			
White Blood Cell Count Decreased (PT) - Gr. 5	0			
Alanine Aminotransferase Increased (PT) - Gr. 3	16			
Alanine Aminotransferase Increased (PT) - Gr. 4	0			
Alanine Aminotransferase Increased (PT) - Gr. 5	0			
Metabolism and Nutrition Disorders (SOC) - Gr. 3	63			
Metabolism and Nutrition Disorders (SOC) - Gr. 4	8			
Metabolism and Nutrition Disorders (SOC) - Gr. 5	1			
Hypokalaemia (PT) - Gr. 3	19			
Hypokalaemia (PT) - Gr. 4	1			
Hypokalaemia (PT) - Gr. 5	0			
Vascular Disorders (SOC) - Gr. 3	62			
Vascular Disorders (SOC) - Gr. 4	2			
Vascular Disorders (SOC) - Gr. 5	0			

Hypertension (PT) - Gr. 3	45			
Hypertension (PT) - Gr. 4	1			
Hypertension (PT) - Gr. 5	0			
Psychiatric Disorders (SOC) - Gr. 3	15			
Psychiatric Disorders (SOC) - Gr. 4	3			
Psychiatric Disorders (SOC) - Gr. 5	1			
Injury, Poisoning & Proced. Complicat. (SOC)-Gr. 3	43			
Injury, Poisoning & Proced. Complicat. (SOC)-Gr. 4	6			
Injury, Poisoning & Proced. Complicat. (SOC)-Gr. 5	0			
Cardiac Disorders (SOC) - Gr. 3	35			
Cardiac Disorders (SOC) - Gr. 4	5			
Cardiac Disorders (SOC) - Gr. 5	7			
Immune System Disorders (SOC) - Gr. 3	17			
Immune System Disorders (SOC) - Gr. 4	1			
Immune System Disorders (SOC) - Gr. 5	0			
Renal and Urinary Disorders (SOC) - Gr. 3	15			
Renal and Urinary Disorders (SOC) - Gr. 4	3			
Renal and Urinary Disorders (SOC) - Gr. 5	0			
Neoplasms Benign, Malignant & Unspec. (SOC) -Gr. 3	13			
Neoplasms Benign, Malignant & Unspec. (SOC) -Gr. 4	5			
Neoplasms Benign, Malignant & Unspec. (SOC) -Gr. 5	0			
Hepatobiliary Disorders (SOC) - Gr. 3	13			
Hepatobiliary Disorders (SOC) - Gr. 4	0			
Hepatobiliary Disorders (SOC) - Gr. 5	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Treatment-Emergent Adverse Events of Any Grade That Were Related to Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥10% of Participants by System Organ Class

End point title	Number of Participants with Treatment-Emergent Adverse Events of Any Grade That Were Related to Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥10% of Participants by System Organ Class[5]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was used to code AEs and the system organ classes are presented in descending order according to the total

frequency of occurrence. If a participant experienced more than one event in a category, they were counted only once in that category.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Any TEAE Related to Pertuzumab (Rel to Ptz)	1037			
Rel to Ptz: Gastrointestinal Disorders	629			
Rel to Ptz: Skin and Subcutaneous Tissue Disorders	491			
Rel to Ptz: Gen. Disorders & Admin.Site Conditions	462			
Rel to Ptz: Investigations	252			
Rel to Ptz: Nervous System Disorders	207			
Rel to Ptz: Resp., Thoracic & Mediast. Disorders	188			
Rel to Ptz: Musculo. & Connective Tissue Disorders	184			
Rel to Ptz: Blood & Lymphatic System Disorders	182			
Rel to Ptz: Infections and Infestations	151			
Any TEAE Related to Trastuzumab (Rel to Trz)	946			
Rel to Trz: Gastrointestinal Disorders	435			
Rel to Trz: Gen. Disorders & Admin.Site Conditions	434			
Rel to Trz: Skin and Subcutaneous Tissue Disorders	384			
Rel to Trz: Investigations	262			
Rel to Trz: Nervous System Disorders	184			
Rel to Trz: Musculo. & Connective Tissue Disorders	179			
Rel to Trz: Blood & Lymphatic System Disorders	163			
Rel to Trz: Resp., Thoracic & Mediast. Disorders	153			
Any TEAE Related to Taxane (Rel to Tax)	1342			
Rel to Tax: Gastrointestinal Disorders	984			
Rel to Tax: Skin and Subcutaneous Tissue Disorders	938			
Rel to Tax: Gen. Disorders & Admin.Site Conditions	834			
Rel to Tax: Nervous System Disorders	764			

Rel to Tax: Blood & Lymphatic System Disorders	457			
Rel to Tax: Musculo. & Connective Tissue Disorders	386			
Rel to Tax: Infections and Infestations	293			
Rel to Tax: Resp., Thoracic & Mediast. Disorders	290			
Rel to Tax: Metabolism and Nutrition Disorders	227			
Rel to Tax: Investigations	201			
Rel to Tax: Eye Disorders	174			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Grade ≥3 Treatment-Emergent Adverse Events That Were Related to Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥0.5% of Participants by Preferred Term

End point title	Number of Participants with Grade ≥3 Treatment-Emergent Adverse Events That Were Related to Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥0.5% of Participants by Preferred Term[6]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was used to code AEs and the preferred terms are presented in descending order according to the total frequency of occurrence. If a participant experienced more than one event in a category, they were counted only once in that category.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

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

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Any Grade ≥3 TEAE Related to Pertuz. (Rel to Ptz)	286			
Rel to Ptz: Diarrhoea	59			
Rel to Ptz: Neutropenia	28			
Rel to Ptz: Febrile Neutropenia	28			
Rel to Ptz: Ejection Fraction Decreased	19			

Rel to Ptz: Neutrophil Count Decreased	15			
Rel to Ptz: Fatigue	15			
Rel to Ptz: Left Ventricular Dysfunction	10			
Rel to Ptz: Asthenia	10			
Rel to Ptz: White Blood Cell Count Decreased	10			
Rel to Ptz: Cardiac Failure	9			
Any Grade ≥3 TEAE Related to Trastuz. (Rel to Trz)	245			
Rel to Trz: Diarrhoea	32			
Rel to Trz: Neutropenia	30			
Rel to Trz: Ejection Fraction Decreased	23			
Rel to Trz: Febrile Neutropenia	21			
Rel to Trz: Neutrophil Count Decreased	15			
Rel to Trz: Fatigue	14			
Rel to Trz: Left Ventricular Dysfunction	11			
Rel to Trz: White Blood Cell Count Decreased	10			
Rel to Trz: Cardiac Failure	8			
Rel to Trz: Asthenia	8			
Any Grade ≥3 TEAE Related to Taxane (Rel to Tax)	514			
Rel to Tax: Neutropenia	140			
Rel to Tax: Febrile Neutropenia	86			
Rel to Tax: Diarrhoea	80			
Rel to Tax: Neutrophil Count Decreased	34			
Rel to Tax: Fatigue	26			
Rel to Tax: Peripheral Neuropathy	24			
Rel to Tax: Asthenia	20			
Rel to Tax: Leukopenia	16			
Rel to Tax: White Blood Cell Count Decreased	16			
Rel to Tax: Mucosal Inflammation	14			
Rel to Tax: Paraesthesia	13			
Rel to Tax: Peripheral Sensory Neuropathy	13			
Rel to Tax: Onycholysis	10			
Rel to Tax: Neutropenic Sepsis	10			
Rel to Tax: Anaemia	10			
Rel to Tax: Vomiting	7			
Rel to Tax: Neurotoxicity	7			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥0.2% of Participants by Preferred Term

End point title	Number of Participants with Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥0.2% of

	Participants by Preferred Term[7]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was used to code AEs and the preferred terms are presented in descending order according to the total frequency of occurrence. If a participant experienced more than one event in a category, they were counted only once in that category. Discont. = discontinuation; Ptz = pertuzumab; Tax = taxane; Trz = trastuzumab

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Any TEAE, Pertuzumab Discontinuation (Ptz Discont)	140			
Ptz Discont: Ejection Fraction Decreased	37			
Ptz Discont: Cardiac Failure	10			
Ptz Discont: Left Ventricular Dysfunction	7			
Ptz Discont: Diarrhoea	7			
Ptz Discont: Dyspnoea	4			
Ptz Discont: Infusion Related Reaction	4			
Ptz Discont: Sepsis	3			
Ptz Discont: Neuropathy Peripheral	3			
Ptz Discont: Hypersensitivity	3			
Ptz Discont: General Physical Health Deterioration	3			
Any TEAE, Trastuzumab Discontinuation(Trz Discont)	133			
Trz Discont: Ejection Fraction Decreased	37			
Trz Discont: Cardiac Failure	10			
Trz Discont: Left Ventricular Dysfunction	7			
Trz Discont: Diarrhoea	6			
Trz Discont: Sepsis	3			
Trz Discont: Dyspnoea	3			
Trz Discont: Neuropathy Peripheral	3			
Trz Discont: Hypersensitivity	3			
Trz Discont: General Physical Health Deterioration	3			
Any TEAE, Taxane Discontinuation (Tax Discont)	286			
Tax Discont: Neuropathy Peripheral	52			

Tax Discont: Peripheral Sensory Neuropathy	25			
Tax Discont: Paraesthesia	24			
Tax Discont: Diarrhoea	19			
Tax Discont: Fatigue	16			
Tax Discont: Asthenia	13			
Tax Discont: Onycholysis	8			
Tax Discont: Nail Toxicity	7			
Tax Discont: Neurotoxicity	7			
Tax Discont: Polyneuropathy	7			
Tax Discont: Oedema Peripheral	7			
Tax Discont: Febrile Neutropenia	7			
Tax Discont: Neutropenia	7			
Tax Discont: Dyspnoea	6			
Tax Discont: Decreased Appetite	6			
Tax Discont: Ejection Fraction Decreased	5			
Tax Discont: General Physical Health Deterioration	4			
Tax Discont: Mucosal Inflammation	4			
Tax Discont: Rash	4			
Tax Discont: Anaemia	4			
Tax Discont: Arthralgia	4			
Tax Discont: Drug Hypersensitivity	4			
Tax Discont: Dysgeusia	3			
Tax Discont: Nail Disorder	3			
Tax Discont: Nail Dystrophy	3			
Tax Discont: Skin Toxicity	3			
Tax Discont: Pneumonia	3			
Tax Discont: Sepsis	3			
Tax Discont: Pleural Effusion	3			
Tax Discont: Pneumonitis	3			
Tax Discont: Cardiac Failure	3			
Tax Discont: Myalgia	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Treatment-Emergent Adverse Events Leading to Dose Interruption of Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥0.5% of Participants by Preferred Term

End point title	Number of Participants with Treatment-Emergent Adverse Events Leading to Dose Interruption of Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥0.5% of Participants by Preferred Term[8]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was

used to code AEs and the preferred terms are presented in descending order according to the total frequency of occurrence. If a participant experienced more than one event in a category, they were counted only once in that category. Interrupt. = interruption; Ptz = pertuzumab; Tax = taxane; Trz = trastuzumab

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[8] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Any TEAE, Pertuzumab Interruption (Ptz Interrupt)	334			
Ptz Interrupt: Ejection Fraction Decreased	51			
Ptz Interrupt: Diarrhoea	21			
Ptz Interrupt: Neutropenia	17			
Ptz Interrupt: Pneumonia	14			
Ptz Interrupt: Upper Respiratory Tract Infection	13			
Ptz Interrupt: Pyrexia	11			
Ptz Interrupt: Dyspnoea	11			
Ptz Interrupt: Drug Hypersensitivity	9			
Ptz Interrupt: Influenza	8			
Ptz Interrupt: Asthenia	8			
Ptz Interrupt: Neutrophil Count Decreased	8			
Ptz Interrupt: Nasopharyngitis	7			
Ptz Interrupt: Anaemia	7			
Any TEAE, Trastuzumab Interruption (Trz Interrupt)	386			
Trz Interrupt: Ejection Fraction Decreased	52			
Trz Interrupt: Drug Hypersensitivity	31			
Trz Interrupt: Diarrhoea	20			
Trz Interrupt: Pyrexia	18			
Trz Interrupt: Neutropenia	17			
Trz Interrupt: Dyspnoea	17			
Trz Interrupt: Pneumonia	14			
Trz Interrupt: Chills	13			
Trz Interrupt: Infusion Related Reaction	13			
Trz Interrupt: Upper Respiratory Tract Infection	12			
Trz Interrupt: Neutrophil Count Decreased	8			
Trz Interrupt: Influenza	7			
Trz Interrupt: Asthenia	7			

Trz Interrupt: Vomiting	7			
Trz Interrupt: Anaemia	7			
Trz Interrupt: Nasopharyngitis	7			
Any TEAE, Taxane Interruption (Tax Interrupt)	354			
Tax Interrupt: Neutropenia	46			
Tax Interrupt: Diarrhoea	30			
Tax Interrupt: Leukopenia	17			
Tax Interrupt: Dyspnoea	15			
Tax Interrupt: Pyrexia	14			
Tax Interrupt: Neutrophil Count Decreased	14			
Tax Interrupt: Ejection Fraction Decreased	13			
Tax Interrupt: Neuropathy Peripheral	13			
Tax Interrupt: Nasopharyngitis	10			
Tax Interrupt: Drug Hypersensitivity	10			
Tax Interrupt: Fatigue	10			
Tax Interrupt: Upper Respiratory Tract Infection	9			
Tax Interrupt: Infusion Related Reaction	9			
Tax Interrupt: Asthenia	9			
Tax Interrupt: Erythema	8			
Tax Interrupt: Pneumonia	7			
Tax Interrupt: Flushing	7			
Tax Interrupt: Hypersensitivity	7			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Treatment-Emergent Adverse Events to Monitor of Any Grade, Occurring in ≥5% of Participants by Category

End point title	Number of Participants with Treatment-Emergent Adverse Events to Monitor of Any Grade, Occurring in ≥5% of Participants by Category[9]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first dose of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, it was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. If a participant had more than one event in a category, they were counted only once in that category. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade ≥3, pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent. MedDRA version 22.1 was used to code AEs; AEs may fall within multiple categories.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[9] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Any TEAE to Monitor	1320			
Infusion-/Administration-Related Reactions	1096			
Rash/Skin Reactions	668			
Mucositis	618			
Cardiac Dysfunction	478			
Neutropenia/Febrile Neutropenia	439			
Anaphylaxis and Hypersensitivity	124			
Diarrhoea Grade ≥3	120			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Grade ≥3 Treatment-Emergent Adverse Events to Monitor, Occurring in ≥0.5% of Participants by Category and Preferred Term

End point title	Number of Participants with Grade ≥3 Treatment-Emergent Adverse Events to Monitor, Occurring in ≥0.5% of Participants by Category and Preferred Term[10]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first dose of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, it was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. If a participant had more than one event in a category, they were counted only once in that category. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade ≥3, pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent. MedDRA version 22.1 was used to code AEs; preferred terms (PT) that are part of a given category are listed in the rows directly below each category within the results table.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[10] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Any Grade ≥3 TEAE to Monitor	535			
Neutropenia/Febrile Neutropenia (Category)	279			
Neutropenia (PT)	145			
Febrile Neutropenia (PT)	90			
Neutrophil Count Decreased (PT)	38			
Leukopenia (PT)	18			
White Blood Cell Count Decreased (PT)	18			
Neutropenic Sepsis (PT)	10			
Infusion-/Admin.-Related Reactions (Category)	123			
Hypertension (PT)	27			
IRR/ARR: Drug Hypersensitivity (PT)	12			
Asthenia (PT)	11			
Fatigue (PT)	11			
Dyspnoea (PT)	10			
Infusion Related Reaction (PT)	8			
Paraesthesia (PT)	7			
Diarrhoea Grade ≥3 (Category)	120			
Diarrhoea (PT)	120			
Cardiac Dysfunction (Category)	51			
Ejection Fraction Decreased (PT)	24			
Left Ventricular Dysfunction (PT)	11			
Cardiac Failure (PT)	9			
Mucositis (Category)	33			
Mucosal Inflammation (PT)	14			
Stomatitis (PT)	9			
Rash/Skin Reactions (Category)	28			
Rash (PT)	10			
Anaphylaxis and Hypersensitivity (Category)	18			
Anaphyl./Hypersens.: Drug Hypersensitivity (PT)	13			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Treatment-Emergent Adverse Events of Special Interest by Category and Preferred Term

End point title	Number of Participants with Treatment-Emergent Adverse Events of Special Interest by Category and Preferred Term[11]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed

as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. TEAEs of special interest included LVEF decreased, liver enzymes (ALT or AST) increased, and suspected transmission of infectious agent by the study drug. MedDRA version 22.1 was used to code AEs; preferred terms (PT) that are part of a given category are listed in the rows directly below each category within the results table. If a participant experienced more than one event in a category, they were counted only once in that category.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[11] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Any TEAE of Special Interest	91			
Decline in LVEF (Category)	90			
Ejection Fraction Decreased (PT)	75			
Left Ventricular Dysfunction (PT)	8			
Cardiac Failure (PT)	7			
Cardiac Failure Congestive (PT)	1			
Elevated ALT or AST (Category)	1			
Hepatic Failure (PT)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Subgroup Analysis by Region of Enrollment: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab

End point title	Subgroup Analysis by Region of Enrollment: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab[12]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2

(0.0-86.4) months.

Notes:

[12] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Europe	Asia	North America	South America
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1009	177	34	121
Units: Percentage of participants				
number (not applicable)				
Any Serious TEAE	38.16	41.81	26.47	30.58
Any TEAE - Grade 3 or Higher (≥3)	62.64	61.58	64.71	52.07
Any Grade ≥3 TEAE Related to Pertuzumab	18.53	24.86	14.71	22.31

End point values	Africa	Other (Australia)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	24		
Units: Percentage of participants				
number (not applicable)				
Any Serious TEAE	22.54	58.33		
Any TEAE - Grade 3 or Higher (≥3)	52.11	66.67		
Any Grade ≥3 TEAE Related to Pertuzumab	26.76	16.67		

Statistical analyses

No statistical analyses for this end point

Primary: Subgroup Analysis by Age (≤65 vs. >65 Years): Overview of Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), TEAEs Leading to Death, Grade ≥3 TEAEs, Any-Grade and Grade ≥3 TEAEs Related to Pertuzumab, and TEAEs to Monitor

End point title	Subgroup Analysis by Age (≤65 vs. >65 Years): Overview of Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), TEAEs Leading to Death, Grade ≥3 TEAEs, Any-Grade and Grade ≥3 TEAEs Related to Pertuzumab, and TEAEs to Monitor[13]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade ≥3, pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[13] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Age ≤65 Years	Age >65 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1167	269		
Units: Percentage of participants				
number (not applicable)				
Any Serious TEAE	35.56	44.61		
Any TEAE Leading to Death	1.46	5.20		
Any TEAE - Grade 3 or Higher (≥3)	58.95	71.00		
Any TEAE Related to Pertuzumab - Any Grade	72.41	71.38		
Any Grade ≥3 TEAE Related to Pertuzumab	19.19	23.05		
Any TEAE to Monitor - Any Grade	92.63	88.85		

Statistical analyses

No statistical analyses for this end point

Primary: Subgroup Analysis by Taxane Chemotherapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), TEAEs Leading to Death, Grade ≥3 TEAEs, Any-Grade and Grade ≥3 TEAEs Related to Pertuzumab, and TEAEs to Monitor

End point title	Subgroup Analysis by Taxane Chemotherapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), TEAEs Leading to Death, Grade ≥3 TEAEs, Any-Grade and Grade ≥3 TEAEs Related to Pertuzumab, and TEAEs to Monitor[14]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade ≥3, pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[14] - 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: There were no formal statistical hypothesis tests to be performed. All results were

summarized by descriptive statistics.

End point values	Docetaxel	Paclitaxel	Nab-Paclitaxel	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	775	588	65	
Units: Percentage of participants				
number (not applicable)				
Any Serious TEAE	38.71	35.71	33.85	
Any TEAE Leading to Death	1.81	2.72	1.54	
Any TEAE - Grade 3 or Higher (≥3)	63.35	59.35	55.38	
Any TEAE Related to Pertuzumab - Any Grade	70.58	73.81	80.00	
Any Grade ≥3 TEAE Related to Pertuzumab	22.06	17.86	13.85	
Any TEAE to Monitor - Any Grade	91.48	92.01	98.46	

Statistical analyses

No statistical analyses for this end point

Primary: Subgroup Analysis by ECOG Performance Status at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab

End point title	Subgroup Analysis by ECOG Performance Status at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab[15]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[15] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	ECOG Performance Status 0 or 1	ECOG Performance Status 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1371	63		
Units: Percentage of participants				
number (not applicable)				

Any Serious TEAE	36.62	52.38		
Any TEAE - Grade 3 or Higher (≥3)	61.05	65.08		
Any Grade ≥3 TEAE Related to Pertuzumab	19.91	20.63		

Statistical analyses

No statistical analyses for this end point

Primary: Subgroup Analysis by Visceral Disease at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab

End point title	Subgroup Analysis by Visceral Disease at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab[16]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[16] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Visceral Disease	Non-Visceral Disease		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	992	444		
Units: Percentage of participants				
number (not applicable)				
Any Serious TEAE	35.58	40.99		
Any TEAE - Grade 3 or Higher (≥3)	61.49	60.59		
Any Grade ≥3 TEAE Related to Pertuzumab	19.86	20.05		

Statistical analyses

No statistical analyses for this end point

Primary: Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab

End point title	Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab[17]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[17] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Prior (Neo)Adjuvant Chemotherapy	No Prior (Neo)Adjuvant Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	786	650		
Units: Percentage of participants				
number (not applicable)				
Any Serious TEAE	36.01	38.77		
Any TEAE - Grade 3 or Higher (≥3)	62.72	59.38		
Any Grade ≥3 TEAE Related to Pertuzumab	21.5	18.00		

Statistical analyses

No statistical analyses for this end point

Primary: Subgroup Analysis by Hormone Receptor Status at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab

End point title	Subgroup Analysis by Hormone Receptor Status at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab[18]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[18] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Hormone Receptor Positive	Hormone Receptor Negative	Hormone Receptor Status Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	918	512	6	
Units: Percentage of participants				
number (not applicable)				
Any Serious TEAE	38.45	34.96	50.00	
Any TEAE - Grade 3 or Higher (≥3)	62.42	59.18	50.00	
Any Grade ≥3 TEAE Related to Pertuzumab	19.72	20.12	33.33	

Statistical analyses

No statistical analyses for this end point

Primary: Subgroup Analysis by Previous Trastuzumab Therapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab

End point title	Subgroup Analysis by Previous Trastuzumab Therapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade ≥3 TEAEs, and Grade ≥3 TEAEs Related to Pertuzumab[19]

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

End point type	Primary

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[19] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Previous Trastuzumab Therapy	No Previous Trastuzumab Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	400	1036		
Units: Percentage of participants				
number (not applicable)				
Any Serious TEAE	33.75	38.61		

Any TEAE - Grade 3 or Higher (≥3)	59.50	61.87		
Any Grade ≥3 TEAE Related to Pertuzumab	19.25	20.17		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with a Congestive Heart Failure Event

End point title	Number of Participants with a Congestive Heart Failure

End point description:

Congestive heart failure was defined as the Standardised MedDRA Query (SMQ) 'Cardiac failure (wide)' from the Medical Dictionary for Regulatory Activities, version 22.1 (MedDRA version 22.1).

End point type	Primary

End point timeframe:

From Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[20] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants	478			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Onset of the First Episode of Congestive Heart Failure

End point title	Time to Onset of the First Episode of Congestive Heart

End point description:

Congestive heart failure was defined as SMQ 'Cardiac failure (wide)' from the MedDRA version 22.1. Time to onset of the first episode of congestive heart failure was analyzed using a Kaplan-Meier approach. Participants who did not experience any congestive heart failure at the time of data-cut were censored at the date of the last attended visit whilst on-treatment (including visits up to and including 28 days after last dose of study treatment). Only treatment emergent congestive heart failure events are included.

End point type	Primary

End point timeframe:

From Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[21] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436[22]			
Units: Months				
median (confidence interval 95%)	999999 (73.82 to 999999)			

Notes:

[22] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Values Over the Course of the Study

End point title	Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Values Over the Course of the Study[23]

End point description:

All participants must have had a baseline LVEF ≥50% to enroll in the study; patients with significant cardiac disease or baseline LVEF below 50% were not eligible for this study. The change from baseline LVEF values were reported at every 3 cycles over the course of the study and at the final treatment, worst treatment, and maximum decrease values. The final treatment value was defined as the last LVEF value observed before all study treatment discontinuation. The worst treatment value was defined as the lowest LVEF value observed before all study treatment discontinuation. The maximum decrease value was defined as the largest decrease of LVEF value from baseline, or minimum increase if a participant's post-baseline LVEF measures were all larger than the baseline value.

End point type	Primary

End point timeframe:

Baseline, predose on Day 1 of every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[23] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436[24]			
Units: Percentage points of LVEF				
arithmetic mean (standard deviation)				
Baseline (BL): Absolute Value at Visit (n = 1435)	64.6 (± 6.46)			
Change from BL at Cycle 3 (n = 1311)	-1.1 (± 6.49)			
Change from BL at Cycle 6 (n = 1248)	-1.5 (± 6.60)			
Change from BL at Cycle 9 (n = 1150)	-2.1 (± 6.56)			
Change from BL at Cycle 12 (n = 1028)	-1.9 (± 6.66)			

Change from BL at Cycle 15 (n = 898)	-2.2 (± 6.50)			
Change from BL at Cycle 18 (n = 816)	-1.8 (± 6.77)			
Change from BL at Cycle 21 (n = 731)	-1.9 (± 6.79)			
Change from BL at Cycle 24 (n = 681)	-1.9 (± 6.93)			
Change from BL at Cycle 27 (n = 633)	-2.1 (± 6.81)			
Change from BL at Cycle 30 (n = 589)	-1.8 (± 6.80)			
Change from BL at Cycle 33 (n = 558)	-1.9 (± 6.97)			
Change from BL at Cycle 36 (n = 509)	-2.1 (± 6.53)			
Change from BL at Cycle 39 (n = 480)	-2.1 (± 6.77)			
Change from BL at Cycle 42 (n = 451)	-1.9 (± 6.52)			
Change from BL at Cycle 45 (n = 428)	-2.2 (± 6.94)			
Change from BL at Cycle 48 (n = 390)	-2.1 (± 6.67)			
Change from BL at Cycle 51 (n = 357)	-1.6 (± 6.75)			
Change from BL at Cycle 54 (n = 325)	-1.7 (± 6.38)			
Change from BL at Cycle 57 (n = 332)	-1.7 (± 6.87)			
Change from BL at Cycle 60 (n = 313)	-1.5 (± 6.46)			
Change from BL at Cycle 63 (n = 302)	-1.6 (± 7.13)			
Change from BL at Cycle 66 (n = 284)	-2.0 (± 6.63)			
Change from BL at Cycle 69 (n = 270)	-1.9 (± 6.45)			
Change from BL at Cycle 72 (n = 259)	-2.1 (± 6.80)			
Change from BL at Cycle 75 (n = 254)	-1.5 (± 6.84)			
Change from BL at Cycle 78 (n = 245)	-1.8 (± 7.41)			
Change from BL at Cycle 81 (n = 226)	-1.8 (± 6.98)			
Change from BL at Cycle 84 (n = 215)	-1.6 (± 6.89)			
Change from BL at Cycle 87 (n = 196)	-1.9 (± 6.31)			
Change from BL at Cycle 90 (n = 177)	-1.1 (± 6.68)			
Change from BL at Cycle 93 (n = 156)	-1.6 (± 6.78)			
Change from BL at Cycle 96 (n = 128)	-1.8 (± 6.33)			
Change from BL at Cycle 99 (n = 106)	-2.0 (± 7.20)			
Change from BL at Cycle 102 (n = 82)	-2.5 (± 7.95)			
Change from BL at Cycle 105 (n = 65)	-2.5 (± 6.86)			
Change from BL at Cycle 108 (n = 49)	-1.8 (± 8.04)			
Change from BL at Cycle 111 (n = 42)	-3.3 (± 7.47)			
Change from BL at Cycle 114 (n = 23)	-1.1 (± 8.12)			
Change from BL at Cycle 117 (n = 17)	-5.8 (± 7.48)			
Change from BL at Cycle 120 (n = 7)	-8.6 (± 6.70)			
Change from BL at Cycle 123 (n = 3)	-9.3 (± 3.51)			
Change from BL at Cycle 126 (n = 1)	-9.0 (± 999999)			
Change from BL at End of Treatment (n = 546)	-3.8 (± 8.34)			
Change from BL at Day 28 of Follow-Up (n = 584)	-3.2 (± 8.19)			
Change from BL: Final Treatment Value (n = 1360)	-2.0 (± 6.77)			
Change from BL: Worst Treatment Value (n = 1360)	-7.1 (± 6.88)			
Change from BL: Maximum Decrease Value (n = 1398)	-7.7 (± 7.45)			

Notes:

[24] - '999999' means the standard deviation could not be calculated with data from a single participant.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants by Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Categories Over the Course of the Study

End point title	Number of Participants by Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Categories Over the Course of the Study[25]

End point description:

All participants must have had a baseline LVEF greater than or equal to (≥)50% to enroll in the study; patients with significant cardiac disease or baseline LVEF below 50% were not eligible for this study. The number of participants are reported according to four change from baseline in LVEF value categories over the course of the study: 1) an increase or decrease from baseline LVEF less than (<)10% points or no change in LVEF; 2) an absolute LVEF value <45% points and a decrease from baseline LVEF ≥10% points to <15% points; 3) an absolute LVEF value <45% points and a decrease from baseline LVEF ≥15% points; or 4) an absolute LVEF value ≥45% points and a decrease from baseline LVEF ≥10% points. BL = baseline; Cyc = cycle; D28FU = Day 28 of follow-up; Dec = decrease; EOT = end of treatment; Inc = increase

End point type	Primary

End point timeframe:

Baseline, predose on Day 1 of every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[25] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Cyc3: Inc/Dec from BL<10% or No Change (n=1311)	1190			
Cyc3: LVEF<45% and Dec from BL ≥10%–<15% (n=1311)	2			
Cyc3: LVEF<45% and Dec from BL ≥15% (n=1311)	5			
Cyc3: LVEF ≥45% and Dec from BL ≥10% (n=1311)	114			
Cyc6: Inc/Dec from BL<10% or No Change (n=1248)	1110			
Cyc6: LVEF<45% and Dec from BL ≥10%–<15% (n=1248)	0			
Cyc6: LVEF<45% and Dec from BL ≥15% (n=1248)	2			
Cyc6: LVEF ≥45% and Dec from BL ≥10% (n=1248)	136			
Cyc9: Inc/Dec from BL<10% or No Change (n=1150)	1005			
Cyc9: LVEF<45% and Dec from BL ≥10%–<15% (n=1150)	2			
Cyc9: LVEF<45% and Dec from BL ≥15% (n=1150)	4			
Cyc9: LVEF ≥45% and Dec from BL ≥10% (n=1150)	139			
Cyc12: Inc/Dec from BL<10% or No Change (n=1028)	906			

Cyc12: LVEF<45% and Dec from BL ≥10%–<15% (n=1028)	0			
Cyc12: LVEF<45% and Dec from BL ≥15% (n=1028)	6			
Cyc12: LVEF ≥45% and Dec from BL ≥10% (n=1028)	116			
Cyc15: Inc/Dec from BL<10% or No Change (n=898)	780			
Cyc15: LVEF<45% and Dec from BL ≥10%–<15% (n=898)	3			
Cyc15: LVEF<45% and Dec from BL ≥15% (n=898)	6			
Cyc15: LVEF ≥45% and Dec from BL ≥10% (n=898)	109			
Cyc18: Inc/Dec from BL<10% or No Change (n=816)	719			
Cyc18: LVEF<45% and Dec from BL ≥10%–<15% (n=816)	0			
Cyc18: LVEF<45% and Dec from BL ≥15% (n=816)	5			
Cyc18: LVEF ≥45% and Dec from BL ≥10% (n=816)	92			
Cyc21: Inc/Dec from BL<10% or No Change (n=731)	639			
Cyc21: LVEF<45% and Dec from BL ≥10%–<15% (n=731)	0			
Cyc21: LVEF<45% and Dec from BL ≥15% (n=731)	4			
Cyc21: LVEF ≥45% and Dec from BL ≥10% (n=731)	88			
Cyc24: Inc/Dec from BL<10% or No Change (n=681)	588			
Cyc24: LVEF<45% and Dec from BL ≥10%–<15% (n=681)	0			
Cyc24: LVEF<45% and Dec from BL ≥15% (n=681)	2			
Cyc24: LVEF ≥45% and Dec from BL ≥10% (n=681)	91			
Cyc27: Inc/Dec from BL<10% or No Change (n=633)	553			
Cyc27: LVEF<45% and Dec from BL ≥10%–<15% (n=633)	0			
Cyc27: LVEF<45% and Dec from BL ≥15% (n=633)	2			
Cyc27: LVEF ≥45% and Dec from BL ≥10% (n=633)	78			
Cyc30: Inc/Dec from BL<10% or No Change (n=589)	518			
Cyc30: LVEF<45% and Dec from BL ≥10%–<15% (n=589)	0			
Cyc30: LVEF<45% and Dec from BL ≥15% (n=589)	1			
Cyc30: LVEF ≥45% and Dec from BL ≥10% (n=589)	70			
Cyc33: Inc/Dec from BL<10% or No Change (n=558)	485			
Cyc33: LVEF<45% and Dec from BL ≥10%–<15% (n=558)	0			
Cyc33: LVEF<45% and Dec from BL ≥15% (n=558)	1			
Cyc33: LVEF ≥45% and Dec from BL ≥10% (n=558)	72			

Cyc36: Inc/Dec from BL<10% or No Change (n=509)	446			
Cyc36: LVEF<45% and Dec from BL ≥10%–<15% (n=509)	0			
Cyc36: LVEF<45% and Dec from BL ≥15% (n=509)	1			
Cyc36: LVEF ≥45% and Dec from BL ≥10% (n=509)	62			
Cyc39: Inc/Dec from BL<10% or No Change (n=480)	414			
Cyc39: LVEF<45% and Dec from BL ≥10%–<15% (n=480)	1			
Cyc39: LVEF<45% and Dec from BL ≥15% (n=480)	0			
Cyc39: LVEF ≥45% and Dec from BL ≥10% (n=480)	65			
Cyc42: Inc/Dec from BL<10% or No Change (n=451)	405			
Cyc42: LVEF<45% and Dec from BL ≥10%–<15% (n=451)	0			
Cyc42: LVEF<45% and Dec from BL ≥15% (n=451)	0			
Cyc42: LVEF ≥45% and Dec from BL ≥10% (n=451)	46			
Cyc45: Inc/Dec from BL<10% or No Change (n=428)	358			
Cyc45: LVEF<45% and Dec from BL ≥10%–<15% (n=428)	0			
Cyc45: LVEF<45% and Dec from BL ≥15% (n=428)	1			
Cyc45: LVEF ≥45% and Dec from BL ≥10% (n=428)	69			
Cyc48: Inc/Dec from BL<10% or No Change (n=390)	340			
Cyc48: LVEF<45% and Dec from BL ≥10%–<15% (n=390)	0			
Cyc48: LVEF<45% and Dec from BL ≥15% (n=390)	1			
Cyc48: LVEF ≥45% and Dec from BL ≥10% (n=390)	49			
Cyc51: Inc/Dec from BL<10% or No Change (n=357)	314			
Cyc51: LVEF<45% and Dec from BL ≥10%–<15% (n=357)	0			
Cyc51: LVEF<45% and Dec from BL ≥15% (n=357)	0			
Cyc51: LVEF ≥45% and Dec from BL ≥10% (n=357)	43			
Cyc54: Inc/Dec from BL<10% or No Change (n=325)	292			
Cyc54: LVEF<45% and Dec from BL ≥10%–<15% (n=325)	0			
Cyc54: LVEF<45% and Dec from BL ≥15% (n=325)	3			
Cyc54: LVEF ≥45% and Dec from BL ≥10% (n=325)	30			
Cyc57: Inc/Dec from BL<10% or No Change (n=332)	291			
Cyc57: LVEF<45% and Dec from BL ≥10%–<15% (n=332)	0			
Cyc57: LVEF<45% and Dec from BL ≥15% (n=332)	0			

Cyc57: LVEF ≥45% and Dec from BL ≥10% (n=332)	41			
Cyc60: Inc/Dec from BL<10% or No Change (n=313)	284			
Cyc60: LVEF<45% and Dec from BL ≥10%–<15% (n=313)	0			
Cyc60: LVEF<45% and Dec from BL ≥15% (n=313)	0			
Cyc60: LVEF ≥45% and Dec from BL ≥10% (n=313)	29			
Cyc63: Inc/Dec from BL<10% or No Change (n=302)	263			
Cyc63: LVEF<45% and Dec from BL ≥10%–<15% (n=302)	0			
Cyc63: LVEF<45% and Dec from BL ≥15% (n=302)	0			
Cyc63: LVEF ≥45% and Dec from BL ≥10% (n=302)	39			
Cyc66: Inc/Dec from BL<10% or No Change (n=284)	249			
Cyc66: LVEF<45% and Dec from BL ≥10%–<15% (n=284)	0			
Cyc66: LVEF<45% and Dec from BL ≥15% (n=284)	0			
Cyc66: LVEF ≥45% and Dec from BL ≥10% (n=284)	35			
Cyc69: Inc/Dec from BL<10% or No Change (n=270)	237			
Cyc69: LVEF<45% and Dec from BL ≥10%–<15% (n=270)	0			
Cyc69: LVEF<45% and Dec from BL ≥15% (n=270)	0			
Cyc69: LVEF ≥45% and Dec from BL ≥10% (n=270)	33			
Cyc72: Inc/Dec from BL<10% or No Change (n=259)	224			
Cyc72: LVEF<45% and Dec from BL ≥10%–<15% (n=259)	0			
Cyc72: LVEF<45% and Dec from BL ≥15% (n=259)	0			
Cyc72: LVEF ≥45% and Dec from BL ≥10% (n=259)	35			
Cyc75: Inc/Dec from BL<10% or No Change (n=254)	224			
Cyc75: LVEF<45% and Dec from BL ≥10%–<15% (n=254)	0			
Cyc75: LVEF<45% and Dec from BL ≥15% (n=254)	1			
Cyc75: LVEF ≥45% and Dec from BL ≥10% (n=254)	29			
Cyc78: Inc/Dec from BL<10% or No Change (n=245)	214			
Cyc78: LVEF<45% and Dec from BL ≥10%–<15% (n=245)	0			
Cyc78: LVEF<45% and Dec from BL ≥15% (n=245)	2			
Cyc78: LVEF ≥45% and Dec from BL ≥10% (n=245)	29			
Cyc81: Inc/Dec from BL<10% or No Change (n=226)	196			
Cyc81: LVEF<45% and Dec from BL ≥10%–<15% (n=226)	0			

Cyc81: LVEF<45% and Dec from BL ≥15% (n=226)	0			
Cyc81: LVEF ≥45% and Dec from BL ≥10% (n=226)	30			
Cyc84: Inc/Dec from BL<10% or No Change (n=215)	192			
Cyc84: LVEF<45% and Dec from BL ≥10%–<15% (n=215)	0			
Cyc84: LVEF<45% and Dec from BL ≥15% (n=215)	0			
Cyc84: LVEF ≥45% and Dec from BL ≥10% (n=215)	23			
Cyc87: Inc/Dec from BL<10% or No Change (n=196)	174			
Cyc87: LVEF<45% and Dec from BL ≥10%–<15% (n=196)	0			
Cyc87: LVEF<45% and Dec from BL ≥15% (n=196)	0			
Cyc87: LVEF ≥45% and Dec from BL ≥10% (n=196)	22			
Cyc90: Inc/Dec from BL<10% or No Change (n=177)	161			
Cyc90: LVEF<45% and Dec from BL ≥10%–<15% (n=177)	0			
Cyc90: LVEF<45% and Dec from BL ≥15% (n=177)	0			
Cyc90: LVEF ≥45% and Dec from BL ≥10% (n=177)	16			
Cyc93: Inc/Dec from BL<10% or No Change (n=156)	140			
Cyc93: LVEF<45% and Dec from BL ≥10%–<15% (n=156)	0			
Cyc93: LVEF<45% and Dec from BL ≥15% (n=156)	0			
Cyc93: LVEF ≥45% and Dec from BL ≥10% (n=156)	16			
Cyc96: Inc/Dec from BL<10% or No Change (n=128)	115			
Cyc96: LVEF<45% and Dec from BL ≥10%–<15% (n=128)	0			
Cyc96: LVEF<45% and Dec from BL ≥15% (n=128)	0			
Cyc96: LVEF ≥45% and Dec from BL ≥10% (n=128)	13			
Cyc99: Inc/Dec from BL<10% or No Change (n=106)	92			
Cyc99: LVEF<45% and Dec from BL ≥10%–<15% (n=106)	0			
Cyc99: LVEF<45% and Dec from BL ≥15% (n=106)	0			
Cyc99: LVEF ≥45% and Dec from BL ≥10% (n=106)	14			
Cyc102: Inc/Dec from BL<10% or No Change (n=82)	68			
Cyc102: LVEF<45% and Dec from BL ≥10%–<15% (n=82)	0			
Cyc102: LVEF<45% and Dec from BL ≥15% (n=82)	0			
Cyc102: LVEF ≥45% and Dec from BL ≥10% (n=82)	14			
Cyc105: Inc/Dec from BL<10% or No Change (n=65)	56			

Cyc105: LVEF<45% and Dec from BL ≥10%–<15% (n=65)	0			
Cyc105: LVEF<45% and Dec from BL ≥15% (n=65)	0			
Cyc105: LVEF ≥45% and Dec from BL ≥10% (n=65)	9			
Cyc108: Inc/Dec from BL<10% or No Change (n=49)	41			
Cyc108: LVEF<45% and Dec from BL ≥10%–<15% (n=49)	0			
Cyc108: LVEF<45% and Dec from BL ≥15% (n=49)	0			
Cyc108: LVEF ≥45% and Dec from BL ≥10% (n=49)	8			
Cyc111: Inc/Dec from BL<10% or No Change (n=42)	34			
Cyc111: LVEF<45% and Dec from BL ≥10%–<15% (n=42)	0			
Cyc111: LVEF<45% and Dec from BL ≥15% (n=42)	0			
Cyc111: LVEF ≥45% and Dec from BL ≥10% (n=42)	8			
Cyc114: Inc/Dec from BL<10% or No Change (n=23)	19			
Cyc114: LVEF<45% and Dec from BL ≥10%–<15% (n=23)	0			
Cyc114: LVEF<45% and Dec from BL ≥15% (n=23)	0			
Cyc114: LVEF ≥45% and Dec from BL ≥10% (n=23)	4			
Cyc117: Inc/Dec from BL<10% or No Change (n=17)	11			
Cyc117: LVEF<45% and Dec from BL ≥10%–<15% (n=17)	0			
Cyc117: LVEF<45% and Dec from BL ≥15% (n=17)	0			
Cyc117: LVEF ≥45% and Dec from BL ≥10% (n=17)	6			
Cyc120: Inc/Dec from BL<10% or No Change (n=7)	4			
Cyc120: LVEF<45% and Dec from BL ≥10%–<15% (n=7)	0			
Cyc120: LVEF<45% and Dec from BL ≥15% (n=7)	0			
Cyc120: LVEF ≥45% and Dec from BL ≥10% (n=7)	3			
Cyc123: Inc/Dec from BL<10% or No Change (n=3)	2			
Cyc123: LVEF<45% and Dec from BL ≥10%–<15% (n=3)	0			
Cyc123: LVEF<45% and Dec from BL ≥15% (n=3)	0			
Cyc123: LVEF ≥45% and Dec from BL ≥10% (n=3)	1			
Cyc126: Inc/Dec from BL<10% or No Change (n=1)	1			
Cyc126: LVEF<45% and Dec from BL ≥10%–<15% (n=1)	0			
Cyc126: LVEF<45% and Dec from BL ≥15% (n=1)	0			
Cyc126: LVEF ≥45% and Dec from BL ≥10% (n=1)	0			

EOT: Inc/Dec from BL<10% or No Change (n=546)	431			
EOT: LVEF<45% and Dec from BL ≥10%–<15% (n=546)	2			
EOT: LVEF<45% and Dec from BL ≥15% (n=546)	26			
EOT: LVEF ≥45% and Dec from BL ≥10% (n=546)	87			
D28FU: Inc/Dec from BL<10% or No Change (n=584)	472			
D28FU: LVEF<45% and Dec from BL ≥10%–<15% (n=584)	4			
D28FU: LVEF<45% and Dec from BL ≥15% (n=584)	22			
D28FU: LVEF ≥45% and Dec from BL ≥10% (n=584)	86			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Laboratory Abnormalities in Hematology and Coagulation Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to NCI-CTC v4.0

End point title	Number of Participants with Laboratory Abnormalities in Hematology and Coagulation Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to NCI-CTC v4.0[26]

End point description:

Clinical laboratory tests for hematology and coagulation parameters were performed at local laboratories. Laboratory toxicities were defined based on NCI-CTC v4.0 from Grades 1 (least severe) to 4 (most severe). Some laboratory parameters are bi-dimensional (i.e. can be graded in both the low and high direction). These parameters were split and presented in both directions. Baseline was defined as the last non-missing measurement taken prior to the first dose of study treatment (including unscheduled assessments). Values from all visits, including unscheduled visits, were included in the derivation of the worst post-baseline grade. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: was clinically significant (per investigator); was accompanied by clinical symptoms; resulted in a change in study treatment; or resulted in a medical intervention or a change in concomitant therapy.

End point type	Primary

End point timeframe:

Predose for each treatment cycle (1 cycle is 3 weeks) from Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[26] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Absolute Neutrophil Count: Normal to Normal	844			

Absolute Neutrophil Count: Normal to Grade 1	232			
Absolute Neutrophil Count: Normal to Grade 2	169			
Absolute Neutrophil Count: Normal to Grade 3	45			
Absolute Neutrophil Count: Normal to Grade 4	27			
Absolute Neutrophil Count: Normal to Missing	27			
Absolute Neutrophil Count: Grade 1 to Normal	3			
Absolute Neutrophil Count: Grade 1 to 1	11			
Absolute Neutrophil Count: Grade 1 to 2	14			
Absolute Neutrophil Count: Grade 1 to 3	3			
Absolute Neutrophil Count: Grade 2 to 1	2			
Absolute Neutrophil Count: Missing to Normal	21			
Absolute Neutrophil Count: Missing to Grade 1	2			
Absolute Neutrophil Count: Missing to Grade 2	3			
Absolute Neutrophil Count: Missing to Grade 4	1			
Absolute Neutrophil Count: Missing to Missing	32			
Hemoglobin (High): Normal to Normal	1327			
Hemoglobin (High): Normal to Grade 1	29			
Hemoglobin (High): Normal to Grade 3	1			
Hemoglobin (High): Normal to Missing	26			
Hemoglobin (High): Grade 1 to Normal	28			
Hemoglobin (High): Grade 1 to 1	5			
Hemoglobin (High): Grade 1 to Missing	2			
Hemoglobin (High): Grade 2 to Normal	1			
Hemoglobin (High): Missing to Normal	14			
Hemoglobin (High): Missing to Missing	3			
Hemoglobin (Low): Normal to Normal	257			
Hemoglobin (Low): Normal to Grade 1	648			
Hemoglobin (Low): Normal to Grade 2	198			
Hemoglobin (Low): Normal to Grade 3	10			
Hemoglobin (Low): Normal to Missing	21			
Hemoglobin (Low): Grade 1 to Normal	2			
Hemoglobin (Low): Grade 1 to 1	109			
Hemoglobin (Low): Grade 1 to 2	128			
Hemoglobin (Low): Grade 1 to 3	12			
Hemoglobin (Low): Grade 1 to Missing	4			
Hemoglobin (Low): Grade 2 to 1	5			
Hemoglobin (Low): Grade 2 to 2	18			
Hemoglobin (Low): Grade 2 to 3	3			
Hemoglobin (Low): Grade 2 to Missing	3			
Hemoglobin (Low): Grade 3 to 1	1			
Hemoglobin (Low): Missing to Normal	3			
Hemoglobin (Low): Missing to Grade 1	7			
Hemoglobin (Low): Missing to Grade 2	4			
Hemoglobin (Low): Missing to Missing	3			

Lymphocytes (High): Normal to Normal	1251			
Lymphocytes (High): Normal to Grade 2	111			
Lymphocytes (High): Normal to Grade 3	8			
Lymphocytes (High): Normal to Missing	28			
Lymphocytes (High): Grade 2 to Normal	4			
Lymphocytes (High): Grade 2 to 2	10			
Lymphocytes (High): Grade 2 to 3	2			
Lymphocytes (High): Grade 3 to Normal	1			
Lymphocytes (High): Grade 3 to 3	2			
Lymphocytes (High): Missing to Normal	15			
Lymphocytes (High): Missing to Grade 2	2			
Lymphocytes (High): Missing to Missing	2			
Lymphocytes (Low): Normal to Normal	565			
Lymphocytes (Low): Normal to Grade 1	255			
Lymphocytes (Low): Normal to Grade 2	210			
Lymphocytes (Low): Normal to Grade 3	76			
Lymphocytes (Low): Normal to Grade 4	18			
Lymphocytes (Low): Normal to Missing	19			
Lymphocytes (Low): Grade 1 to Normal	11			
Lymphocytes (Low): Grade 1 to 1	54			
Lymphocytes (Low): Grade 1 to 2	51			
Lymphocytes (Low): Grade 1 to 3	18			
Lymphocytes (Low): Grade 1 to 4	6			
Lymphocytes (Low): Grade 1 to Missing	5			
Lymphocytes (Low): Grade 2 to Normal	12			
Lymphocytes (Low): Grade 2 to 1	8			
Lymphocytes (Low): Grade 2 to 2	37			
Lymphocytes (Low): Grade 2 to 3	19			
Lymphocytes (Low): Grade 2 to 4	1			
Lymphocytes (Low): Grade 2 to Missing	2			
Lymphocytes (Low): Grade 3 to 1	3			
Lymphocytes (Low): Grade 3 to 2	8			
Lymphocytes (Low): Grade 3 to 3	14			
Lymphocytes (Low): Grade 3 to 4	2			
Lymphocytes (Low): Grade 3 to Missing	1			
Lymphocytes (Low): Grade 4 to 2	1			
Lymphocytes (Low): Grade 4 to 3	3			
Lymphocytes (Low): Grade 4 to 4	16			
Lymphocytes (Low): Grade 4 to Missing	1			
Lymphocytes (Low): Missing to Normal	11			
Lymphocytes (Low): Missing to Grade 1	3			
Lymphocytes (Low): Missing to Grade 2	3			
Lymphocytes (Low): Missing to Grade 3	1			
Lymphocytes (Low): Missing to Missing	2			
Platelet Count: Normal to Normal	1222			
Platelet Count: Normal to Grade 1	149			
Platelet Count: Normal to Grade 3	1			
Platelet Count: Normal to Grade 4	2			
Platelet Count: Normal to Missing	26			
Platelet Count: Grade 1 to Normal	15			
Platelet Count: Grade 1 to 1	16			
Platelet Count: Grade 1 to 2	1			

Platelet Count: Grade 1 to Missing	2			
Platelet Count: Missing to Normal	1			
Platelet Count: Missing to Grade 1	1			
White Blood Cells (High): Normal to Normal	1391			
White Blood Cells (High): Normal to Missing	29			
White Blood Cells (High): Missing to Normal	14			
White Blood Cells (High): Missing to Missing	2			
White Blood Cells (Low): Normal to Normal	702			
White Blood Cells (Low): Normal to Grade 1	392			
White Blood Cells (Low): Normal to Grade 2	190			
White Blood Cells (Low): Normal to Grade 3	29			
White Blood Cells (Low): Normal to Grade 4	6			
White Blood Cells (Low): Normal to Missing	29			
White Blood Cells (Low): Grade 1 to Normal	4			
White Blood Cells (Low): Grade 1 to 1	20			
White Blood Cells (Low): Grade 1 to 2	33			
White Blood Cells (Low): Grade 1 to 3	4			
White Blood Cells (Low): Grade 2 to Normal	2			
White Blood Cells (Low): Grade 2 to 1	4			
White Blood Cells (Low): Grade 2 to 2	3			
White Blood Cells (Low): Grade 3 to Normal	1			
White Blood Cells (Low): Grade 3 to 3	1			
White Blood Cells (Low): Missing to Normal	9			
White Blood Cells (Low): Missing to Grade 1	3			
White Blood Cells (Low): Missing to Grade 2	1			
White Blood Cells (Low): Missing to Grade 3	1			
White Blood Cells (Low): Missing to Missing	2			
International Normalized Ratio: Normal to Normal	17			
International Normalized Ratio: Normal to Grade 1	52			
International Normalized Ratio: Normal to Grade 2	1			
International Normalized Ratio: Normal to Missing	3			
International Normalized Ratio: Grade 1 to Normal	1			
International Normalized Ratio: Grade 2 to 3	1			
International Normalized Ratio: Missing to Normal	424			

International Normalized Ratio: Missing to Grade 1	615			
International Normalized Ratio: Missing to Grade 2	23			
International Normalized Ratio: Missing to Grade 3	14			
International Normalized Ratio: Missing to Missing	285			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Laboratory Abnormalities in Hematology and Coagulation Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to Normal Range Criteria

End point title	Number of Participants with Laboratory Abnormalities in Hematology and Coagulation Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to Normal Range Criteria[27]

End point description:

Clinical laboratory tests for hematology and coagulation parameters were performed at local laboratories. Laboratory toxicities were defined based on local laboratory normal ranges (for parameters with NCI-CTC grade not defined). Some laboratory parameters are bi-dimensional (i.e. can be graded in both the low and high direction). These parameters were split and presented in both directions. Baseline was defined as the last non-missing measurement taken prior to the first dose of study treatment (including unscheduled assessments). Values from all visits, including unscheduled visits, were included in the derivation of the worst post-baseline grade. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: was clinically significant (per investigator); was accompanied by clinical symptoms; resulted in a change in study treatment; or resulted in a medical intervention or a change in concomitant therapy.

End point type	Primary

End point timeframe:

Predose for each treatment cycle (1 cycle is 3 weeks) from Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[27] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Basophils (High): Normal to Normal	1020			
Basophils (High): Normal to Low	3			
Basophils (High): Normal to High	261			
Basophils (High): Low to Normal	16			
Basophils (High): Low to Low	1			
Basophils (High): Low to High	5			
Basophils (High): High to Normal	11			
Basophils (High): High to High	38			

Basophils (High): Missing to Normal	21			
Basophils (High): Missing to High	7			
Basophils (High): Missing to Missing	53			
Basophils (Low): Normal to Normal	1206			
Basophils (Low): Normal to Low	77			
Basophils (Low): Normal to High	1			
Basophils (Low): Low to Normal	3			
Basophils (Low): Low to Low	18			
Basophils (Low): Low to Missing	1			
Basophils (Low): High to Normal	36			
Basophils (Low): High to Low	5			
Basophils (Low): High to High	8			
Basophils (Low): Missing to Normal	40			
Basophils (Low): Missing to Low	3			
Basophils (Low): Missing to High	1			
Basophils (Low): Missing to Missing	37			
Eosinophils (High): Normal to Normal	904			
Eosinophils (High): Normal to Low	13			
Eosinophils (High): Normal to High	283			
Eosinophils (High): Low to Normal	66			
Eosinophils (High): Low to Low	13			
Eosinophils (High): Low to High	36			
Eosinophils (High): High to Normal	11			
Eosinophils (High): High to High	35			
Eosinophils (High): Missing to Normal	17			
Eosinophils (High): Missing to Low	1			
Eosinophils (High): Missing to High	7			
Eosinophils (High): Missing to Missing	50			
Eosinophils (Low): Normal to Normal	810			
Eosinophils (Low): Normal to Low	390			
Eosinophils (Low): Low to Normal	13			
Eosinophils (Low): Low to Low	101			
Eosinophils (Low): Low to High	1			
Eosinophils (Low): High to Normal	28			
Eosinophils (Low): High to Low	13			
Eosinophils (Low): High to High	5			
Eosinophils (Low): Missing to Normal	37			
Eosinophils (Low): Missing to Low	10			
Eosinophils (Low): Missing to Missing	28			
Hematocrit (High): Normal to Normal	953			
Hematocrit (High): Normal to Low	47			
Hematocrit (High): Normal to High	58			
Hematocrit (High): Normal to Missing	4			
Hematocrit (High): Low to Normal	201			
Hematocrit (High): Low to Low	97			
Hematocrit (High): Low to High	10			
Hematocrit (High): Low to Missing	2			
Hematocrit (High): High to Normal	17			
Hematocrit (High): High to High	12			
Hematocrit (High): Missing to Normal	15			
Hematocrit (High): Missing to High	1			
Hematocrit (High): Missing to Missing	19			

Hematocrit (Low): Normal to Normal	223			
Hematocrit (Low): Normal to Low	837			
Hematocrit (Low): Normal to Missing	2			
Hematocrit (Low): Low to Normal	5			
Hematocrit (Low): Low to Low	305			
Hematocrit (Low): High to Normal	13			
Hematocrit (Low): High to Low	16			
Hematocrit (Low): Missing to Normal	3			
Hematocrit (Low): Missing to Low	12			
Hematocrit (Low): Missing to Missing	20			
Monocytes (High): Normal to Normal	802			
Monocytes (High): Normal to Low	3			
Monocytes (High): Normal to High	365			
Monocytes (High): Low to Normal	58			
Monocytes (High): Low to Low	6			
Monocytes (High): Low to High	17			
Monocytes (High): High to Normal	29			
Monocytes (High): High to Low	1			
Monocytes (High): High to High	82			
Monocytes (High): Missing to Normal	12			
Monocytes (High): Missing to High	8			
Monocytes (High): Missing to Missing	53			
Monocytes (Low): Normal to Normal	747			
Monocytes (Low): Normal to Low	420			
Monocytes (Low): Normal to High	3			
Monocytes (Low): Low to Normal	11			
Monocytes (Low): Low to Low	70			
Monocytes (Low): High to Normal	64			
Monocytes (Low): High to Low	40			
Monocytes (Low): High to High	8			
Monocytes (Low): Missing to Normal	13			
Monocytes (Low): Missing to Low	10			
Monocytes (Low): Missing to High	5			
Monocytes (Low): Missing to Missing	45			
Red Blood Cells (High): Normal to Normal	975			
Red Blood Cells (High): Normal to Low	31			
Red Blood Cells (High): Normal to High	111			
Red Blood Cells (High): Low to Normal	131			
Red Blood Cells (High): Low to Low	61			
Red Blood Cells (High): Low to High	15			
Red Blood Cells (High): High to Normal	22			
Red Blood Cells (High): High to High	45			
Red Blood Cells (High): Missing to Normal	18			
Red Blood Cells (High): Missing to Low	2			
Red Blood Cells (High): Missing to High	2			
Red Blood Cells (High): Missing to Missing	23			
Red Blood Cells (Low): Normal to Normal	350			
Red Blood Cells (Low): Normal to Low	767			
Red Blood Cells (Low): Low to Normal	10			

Red Blood Cells (Low): Low to Low	197			
Red Blood Cells (Low): High to Normal	44			
Red Blood Cells (Low): High to Low	21			
Red Blood Cells (Low): High to High	2			
Red Blood Cells (Low): Missing to Normal	6			
Red Blood Cells (Low): Missing to Low	16			
Red Blood Cells (Low): Missing to Missing	23			
PTT (High): Normal to Normal	46			
PTT (High): Normal to Low	1			
PTT (High): Normal to High	15			
PTT (High): Low to Normal	19			
PTT (High): Low to Low	1			
PTT (High): Low to High	1			
PTT (High): High to High	1			
PTT (High): Missing to Normal	19			
PTT (High): Missing to Low	5			
PTT (High): Missing to High	9			
PTT (High): Missing to Missing	1319			
PTT (Low): Normal to Normal	46			
PTT (Low): Normal to Low	16			
PTT (Low): Low to Normal	3			
PTT (Low): Low to Low	18			
PTT (Low): High to Normal	1			
PTT (Low): Missing to Normal	20			
PTT (Low): Missing to Low	6			
PTT (Low): Missing to High	5			
PTT (Low): Missing to Missing	1321			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Laboratory Abnormalities in Biochemistry Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to NCI-CTC v4.0

End point title	Number of Participants with Laboratory Abnormalities in Biochemistry Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to NCI-CTC v4.0[28]

End point description:

Clinical laboratory tests for biochemistry parameters were performed at local laboratories. Laboratory toxicities were defined based on NCI-CTC v4.0 from Grades 1 (least severe) to 4 (most severe). Some laboratory parameters are bi-dimensional (i.e. can be graded in both the low and high direction). These parameters were split and presented in both directions. Baseline was defined as the last non-missing measurement taken prior to the first dose of study treatment (including unscheduled assessments). Values from all visits, including unscheduled visits, were included in the derivation of the worst post-baseline grade. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: was clinically significant (per investigator); was accompanied by clinical symptoms; resulted in a change in study treatment; or resulted in a medical intervention or a change in concomitant therapy.

End point type	Primary

End point timeframe:

Predose for each treatment cycle (1 cycle is 3 weeks) from Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[28] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Alanine Aminotransferase: Normal to Normal	610			
Alanine Aminotransferase: Normal to Grade 1	425			
Alanine Aminotransferase: Normal to Grade 2	26			
Alanine Aminotransferase: Normal to Grade 3	19			
Alanine Aminotransferase: Normal to Missing	25			
Alanine Aminotransferase: Grade 1 to Normal	75			
Alanine Aminotransferase: Grade 1 to 1	151			
Alanine Aminotransferase: Grade 1 to 2	26			
Alanine Aminotransferase: Grade 1 to 3	14			
Alanine Aminotransferase: Grade 1 to Missing	6			
Alanine Aminotransferase: Grade 2 to Normal	8			
Alanine Aminotransferase: Grade 2 to 1	28			
Alanine Aminotransferase: Grade 2 to 2	5			
Alanine Aminotransferase: Grade 2 to 3	1			
Alanine Aminotransferase: Grade 3 to 1	2			
Alanine Aminotransferase: Missing to Normal	7			
Alanine Aminotransferase: Missing to Grade 1	4			
Alanine Aminotransferase: Missing to Grade 2	1			
Alanine Aminotransferase: Missing to Missing	3			
Aspartate Aminotransferase: Normal to Normal	562			
Aspartate Aminotransferase: Normal to Grade 1	386			
Aspartate Aminotransferase: Normal to Grade 2	22			
Aspartate Aminotransferase: Normal to Grade 3	9			
Aspartate Aminotransferase: Normal to Missing	15			
Aspartate Aminotransferase: Grade 1 to Normal	120			

Aspartate Aminotransferase: Grade 1 to 1	187			
Aspartate Aminotransferase: Grade 1 to 2	24			
Aspartate Aminotransferase: Grade 1 to 3	9			
Aspartate Aminotransferase: Grade 1 to Missing	14			
Aspartate Aminotransferase: Grade 2 to Normal	13			
Aspartate Aminotransferase: Grade 2 to 1	29			
Aspartate Aminotransferase: Grade 2 to 2	3			
Aspartate Aminotransferase: Grade 2 to Missing	3			
Aspartate Aminotransferase: Grade 3 to Normal	2			
Aspartate Aminotransferase: Grade 3 to 1	7			
Aspartate Aminotransferase: Grade 3 to Missing	1			
Aspartate Aminotransferase: Missing to Normal	13			
Aspartate Aminotransferase: Missing to Grade 1	9			
Aspartate Aminotransferase: Missing to Grade 2	2			
Aspartate Aminotransferase: Missing to Missing	6			
Albumin: Normal to Normal	785			
Albumin: Normal to Grade 1	357			
Albumin: Normal to Grade 2	86			
Albumin: Normal to Grade 3	10			
Albumin: Normal to Missing	23			
Albumin: Grade 1 to Normal	13			
Albumin: Grade 1 to 1	43			
Albumin: Grade 1 to 2	35			
Albumin: Grade 1 to 3	1			
Albumin: Grade 1 to Missing	7			
Albumin: Grade 2 to Normal	3			
Albumin: Grade 2 to 1	5			
Albumin: Grade 2 to 2	8			
Albumin: Grade 2 to 3	2			
Albumin: Grade 2 to Missing	2			
Albumin: Grade 3 to 2	1			
Albumin: Grade 3 to Missing	1			
Albumin: Missing to Normal	28			
Albumin: Missing to Grade 1	14			
Albumin: Missing to Grade 2	6			
Albumin: Missing to Missing	6			
Alkaline Phosphatase: Normal to Normal	605			
Alkaline Phosphatase: Normal to Grade 1	329			
Alkaline Phosphatase: Normal to Grade 2	14			
Alkaline Phosphatase: Normal to Grade 3	2			

Alkaline Phosphatase: Normal to Missing	18			
Alkaline Phosphatase: Grade 1 to Normal	44			
Alkaline Phosphatase: Grade 1 to 1	241			
Alkaline Phosphatase: Grade 1 to 2	72			
Alkaline Phosphatase: Grade 1 to 3	15			
Alkaline Phosphatase: Grade 1 to Missing	6			
Alkaline Phosphatase: Grade 2 to Normal	2			
Alkaline Phosphatase: Grade 2 to 1	21			
Alkaline Phosphatase: Grade 2 to 2	24			
Alkaline Phosphatase: Grade 2 to 3	14			
Alkaline Phosphatase: Grade 2 to Missing	8			
Alkaline Phosphatase: Grade 3 to 1	2			
Alkaline Phosphatase: Grade 3 to 2	1			
Alkaline Phosphatase: Grade 3 to 3	4			
Alkaline Phosphatase: Missing to Normal	7			
Alkaline Phosphatase: Missing to Grade 1	3			
Alkaline Phosphatase: Missing to Grade 3	1			
Alkaline Phosphatase: Missing to Missing	3			
Calcium (High): Normal to Normal	1060			
Calcium (High): Normal to Grade 1	192			
Calcium (High): Normal to Grade 2	2			
Calcium (High): Normal to Grade 3	1			
Calcium (High): Normal to Grade 4	1			
Calcium (High): Normal to Missing	26			
Calcium (High): Grade 1 to Normal	47			
Calcium (High): Grade 1 to 1	47			
Calcium (High): Grade 1 to 2	1			
Calcium (High): Grade 1 to 3	1			
Calcium (High): Grade 1 to Missing	5			
Calcium (High): Grade 2 to Normal	1			
Calcium (High): Grade 2 to 1	1			
Calcium (High): Grade 2 to 2	1			
Calcium (High): Grade 3 to Normal	2			
Calcium (High): Grade 3 to 1	1			
Calcium (High): Grade 3 to 2	1			
Calcium (High): Grade 4 to Normal	1			
Calcium (High): Missing to Normal	32			
Calcium (High): Missing to Grade 1	3			
Calcium (High): Missing to Missing	10			
Calcium (Low): Normal to Normal	786			
Calcium (Low): Normal to Grade 1	378			
Calcium (Low): Normal to Grade 2	117			
Calcium (Low): Normal to Grade 3	18			
Calcium (Low): Normal to Missing	30			
Calcium (Low): Grade 1 to Normal	5			
Calcium (Low): Grade 1 to 1	31			
Calcium (Low): Grade 1 to 2	12			
Calcium (Low): Grade 1 to 3	2			

Calcium (Low): Grade 1 to Missing	1			
Calcium (Low): Grade 2 to Normal	5			
Calcium (Low): Grade 2 to 1	1			
Calcium (Low): Grade 2 to 2	4			
Calcium (Low): Grade 3 to 3	1			
Calcium (Low): Missing to Normal	20			
Calcium (Low): Missing to Grade 1	11			
Calcium (Low): Missing to Grade 2	4			
Calcium (Low): Missing to Missing	10			
Creatinine: Normal to Normal	176			
Creatinine: Normal to Grade 1	960			
Creatinine: Normal to Grade 2	175			
Creatinine: Normal to Grade 3	5			
Creatinine: Normal to Grade 4	5			
Creatinine: Normal to Missing	26			
Creatinine: Grade 1 to Normal	12			
Creatinine: Grade 1 to 1	38			
Creatinine: Grade 1 to 2	8			
Creatinine: Grade 1 to Missing	3			
Creatinine: Grade 2 to 2	3			
Creatinine: Grade 2 to 3	1			
Creatinine: Grade 2 to Missing	1			
Creatinine: Missing to Normal	11			
Creatinine: Missing to Grade 1	6			
Creatinine: Missing to Missing	6			
Gamma-Glutamyl Transpeptidase: Normal to Normal	498			
Gamma-Glutamyl Transpeptidase: Normal to Grade 1	227			
Gamma-Glutamyl Transpeptidase: Normal to Grade 2	39			
Gamma-Glutamyl Transpeptidase: Normal to Grade 3	15			
Gamma-Glutamyl Transpeptidase: Normal to Missing	12			
Gamma-Glutamyl Transpeptidase: Grade 1 to Normal	64			
Gamma-Glutamyl Transpeptidase: Grade 1 to 1	187			
Gamma-Glutamyl Transpeptidase: Grade 1 to 2	75			
Gamma-Glutamyl Transpeptidase: Grade 1 to 3	20			
Gamma-Glutamyl Transpeptidase: Grade 1 to Missing	7			
Gamma-Glutamyl Transpeptidase: Grade 2 to Normal	5			
Gamma-Glutamyl Transpeptidase: Grade 2 to 1	52			
Gamma-Glutamyl Transpeptidase: Grade 2 to 2	45			
Gamma-Glutamyl Transpeptidase: Grade 2 to 3	21			
Gamma-Glutamyl Transpeptidase: Grade 2 to Missing	5			
Gamma-Glutamyl Transpeptidase: Grade 3 to Normal	2			

Gamma-Glutamyl Transpeptidase: Grade 3 to 1	15			
Gamma-Glutamyl Transpeptidase: Grade 3 to 2	38			
Gamma-Glutamyl Transpeptidase: Grade 3 to 3	47			
Gamma-Glutamyl Transpeptidase: Grade 3 to Missing	4			
Gamma-Glutamyl Transpeptidase: Missing to Normal	14			
Gamma-Glutamyl Transpeptidase: Missing to Grade 1	7			
Gamma-Glutamyl Transpeptidase: Missing to Grade 2	10			
Gamma-Glutamyl Transpeptidase: Missing to Grade 3	18			
Gamma-Glutamyl Transpeptidase: Missing to Missing	9			
Glucose (High): Normal to Normal	340			
Glucose (High): Normal to Grade 1	534			
Glucose (High): Normal to Grade 2	115			
Glucose (High): Normal to Missing	21			
Glucose (High): Grade 1 to Normal	28			
Glucose (High): Grade 1 to 1	190			
Glucose (High): Grade 1 to 2	74			
Glucose (High): Grade 1 to Missing	9			
Glucose (High): Grade 2 to Normal	2			
Glucose (High): Grade 2 to 1	13			
Glucose (High): Grade 2 to 2	10			
Glucose (High): Grade 2 to Missing	3			
Glucose (High): Missing to Normal	20			
Glucose (High): Missing to Grade 1	30			
Glucose (High): Missing to Grade 2	40			
Glucose (High): Missing to Missing	7			
Glucose (Low): Normal to Normal	1061			
Glucose (Low): Normal to Grade 1	173			
Glucose (Low): Normal to Grade 2	19			
Glucose (Low): Normal to Grade 3	4			
Glucose (Low): Normal to Grade 4	5			
Glucose (Low): Normal to Missing	33			
Glucose (Low): Grade 1 to Normal	8			
Glucose (Low): Grade 1 to 1	24			
Glucose (Low): Grade 1 to 2	3			
Glucose (Low): Grade 1 to 3	1			
Glucose (Low): Grade 1 to 4	1			
Glucose (Low): Grade 2 to Normal	1			
Glucose (Low): Missing to Normal	69			
Glucose (Low): Missing to Grade 1	16			
Glucose (Low): Missing to Grade 2	2			
Glucose (Low): Missing to Grade 3	1			
Glucose (Low): Missing to Missing	15			
Magnesium (High): Normal to Normal	1100			
Magnesium (High): Normal to Grade 1	122			
Magnesium (High): Normal to Grade 3	38			
Magnesium (High): Normal to Grade 4	6			

Magnesium (High): Normal to Missing	31			
Magnesium (High): Grade 1 to Normal	12			
Magnesium (High): Grade 1 to 1	7			
Magnesium (High): Grade 3 to Normal	2			
Magnesium (High): Grade 3 to 3	2			
Magnesium (High): Grade 4 to Normal	1			
Magnesium (High): Grade 4 to 4	1			
Magnesium (High): Missing to Normal	85			
Magnesium (High): Missing to Grade 1	12			
Magnesium (High): Missing to Grade 3	6			
Magnesium (High): Missing to Missing	11			
Magnesium (Low): Normal to Normal	857			
Magnesium (Low): Normal to Grade 1	319			
Magnesium (Low): Normal to Grade 2	28			
Magnesium (Low): Normal to Grade 3	9			
Magnesium (Low): Normal to Grade 4	3			
Magnesium (Low): Normal to Missing	28			
Magnesium (Low): Grade 1 to Normal	9			
Magnesium (Low): Grade 1 to 1	55			
Magnesium (Low): Grade 1 to 2	7			
Magnesium (Low): Grade 1 to 3	3			
Magnesium (Low): Grade 1 to Missing	3			
Magnesium (Low): Grade 4 to 4	1			
Magnesium (Low): Missing to Normal	81			
Magnesium (Low): Missing to Grade 1	19			
Magnesium (Low): Missing to Grade 2	1			
Magnesium (Low): Missing to Grade 3	1			
Magnesium (Low): Missing to Grade 4	1			
Magnesium (Low): Missing to Missing	11			
Potassium (High): Normal to Normal	1051			
Potassium (High): Normal to Grade 1	183			
Potassium (High): Normal to Grade 2	81			
Potassium (High): Normal to Grade 3	18			
Potassium (High): Normal to Grade 4	8			
Potassium (High): Normal to Missing	26			
Potassium (High): Grade 1 to Normal	16			
Potassium (High): Grade 1 to 1	8			
Potassium (High): Grade 1 to 2	7			
Potassium (High): Grade 1 to 3	1			
Potassium (High): Grade 1 to Missing	3			
Potassium (High): Grade 2 to Normal	2			
Potassium (High): Grade 2 to 1	1			
Potassium (High): Grade 2 to 2	1			
Potassium (High): Grade 4 to Normal	1			
Potassium (High): Missing to Normal	18			
Potassium (High): Missing to Grade 1	5			
Potassium (High): Missing to Grade 2	3			
Potassium (High): Missing to Missing	3			
Potassium (Low): Normal to Normal	990			
Potassium (Low): Normal to Grade 2	367			
Potassium (Low): Normal to Missing	29			
Potassium (Low): Grade 2 to Normal	8			

Potassium (Low): Grade 2 to 2	13			
Potassium (Low): Missing to Normal	19			
Potassium (Low): Missing to Grade 2	7			
Potassium (Low): Missing to Missing	3			
Sodium (High): Normal to Normal	1075			
Sodium (High): Normal to Grade 1	256			
Sodium (High): Normal to Grade 2	36			
Sodium (High): Normal to Grade 3	9			
Sodium (High): Normal to Grade 4	1			
Sodium (High): Normal to Missing	28			
Sodium (High): Grade 1 to Normal	3			
Sodium (High): Grade 1 to 1	6			
Sodium (High): Grade 1 to 2	3			
Sodium (High): Grade 1 to 3	1			
Sodium (High): Grade 2 to 2	2			
Sodium (High): Grade 2 to 3	1			
Sodium (High): Grade 3 to Normal	1			
Sodium (High): Grade 3 to Missing	1			
Sodium (High): Missing to Normal	11			
Sodium (High): Missing to Grade 1	1			
Sodium (High): Missing to Missing	1			
Sodium (Low): Normal to Normal	994			
Sodium (Low): Normal to Grade 1	298			
Sodium (Low): Normal to Grade 3	20			
Sodium (Low): Normal to Grade 4	15			
Sodium (Low): Normal to Missing	23			
Sodium (Low): Grade 1 to Normal	21			
Sodium (Low): Grade 1 to 1	36			
Sodium (Low): Grade 1 to 3	2			
Sodium (Low): Grade 1 to 4	1			
Sodium (Low): Grade 1 to Missing	6			
Sodium (Low): Grade 3 to Normal	1			
Sodium (Low): Grade 3 to 1	2			
Sodium (Low): Grade 3 to 3	1			
Sodium (Low): Grade 4 to Normal	2			
Sodium (Low): Grade 4 to 1	1			
Sodium (Low): Missing to Normal	6			
Sodium (Low): Missing to Grade 1	5			
Sodium (Low): Missing to Grade 3	1			
Sodium (Low): Missing to Missing	1			
Total Bilirubin: Normal to Normal	1231			
Total Bilirubin: Normal to Grade 1	88			
Total Bilirubin: Normal to Grade 2	35			
Total Bilirubin: Normal to Grade 3	2			
Total Bilirubin: Normal to Missing	28			
Total Bilirubin: Grade 1 to Normal	3			
Total Bilirubin: Grade 1 to 1	11			
Total Bilirubin: Grade 1 to 2	6			
Total Bilirubin: Grade 1 to Missing	2			
Total Bilirubin: Grade 2 to 1	1			
Total Bilirubin: Grade 2 to 2	1			
Total Bilirubin: Grade 2 to Missing	1			

Total Bilirubin: Grade 3 to Normal	1			
Total Bilirubin: Missing to Normal	22			
Total Bilirubin: Missing to Grade 2	1			
Total Bilirubin: Missing to Missing	3			
Uric Acid: Normal to Normal	933			
Uric Acid: Normal to Grade 1	190			
Uric Acid: Normal to Grade 4	8			
Uric Acid: Normal to Missing	20			
Uric Acid: Grade 1 to Normal	58			
Uric Acid: Grade 1 to 1	120			
Uric Acid: Grade 1 to 4	6			
Uric Acid: Grade 1 to Missing	11			
Uric Acid: Grade 4 to Normal	1			
Uric Acid: Grade 4 to 1	2			
Uric Acid: Grade 4 to 4	4			
Uric Acid: Grade 4 to Missing	1			
Uric Acid: Missing to Normal	57			
Uric Acid: Missing to Grade 1	13			
Uric Acid: Missing to Grade 4	2			
Uric Acid: Missing to Missing	10			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Laboratory Abnormalities in Biochemistry Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to Normal Range Criteria

End point title	Number of Participants with Laboratory Abnormalities in Biochemistry Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to Normal Range Criteria[29]

End point description:

Clinical laboratory tests for biochemistry parameters were performed at local laboratories. Laboratory toxicities were defined based on local laboratory normal ranges (for parameters with NCI-CTC grade not defined). Some laboratory parameters are bi-dimensional (i.e. can be graded in both the low and high direction). These parameters were split and presented in both directions. Baseline was defined as the last non-missing measurement taken prior to the first dose of study treatment (including unscheduled assessments). Values from all visits, including unscheduled visits, were included in the derivation of the worst post-baseline grade. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: was clinically significant (per investigator); was accompanied by clinical symptoms; resulted in a change in study treatment; or resulted in a medical intervention or a change in concomitant therapy.

End point type	Primary

End point timeframe:

Predose for each treatment cycle (1 cycle is 3 weeks) from Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[29] - 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: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Participants				
Blood Urea Nitrogen (High): Normal to Normal	717			
Blood Urea Nitrogen (High): Normal to Low	5			
Blood Urea Nitrogen (High): Normal to High	402			
Blood Urea Nitrogen (High): Normal to Missing	2			
Blood Urea Nitrogen (High): Low to Normal	69			
Blood Urea Nitrogen (High): Low to Low	8			
Blood Urea Nitrogen (High): Low to High	12			
Blood Urea Nitrogen (High): High to Normal	23			
Blood Urea Nitrogen (High): High to High	98			
Blood Urea Nitrogen (High): Missing to Normal	42			
Blood Urea Nitrogen (High): Missing to High	19			
Blood Urea Nitrogen (High): Missing to Missing	39			
Blood Urea Nitrogen (Low): Normal to Normal	828			
Blood Urea Nitrogen (Low): Normal to Low	293			
Blood Urea Nitrogen (Low): Normal to High	3			
Blood Urea Nitrogen (Low): Normal to Missing	2			
Blood Urea Nitrogen (Low): Low to Normal	17			
Blood Urea Nitrogen (Low): Low to Low	72			
Blood Urea Nitrogen (Low): High to Normal	104			
Blood Urea Nitrogen (Low): High to Low	11			
Blood Urea Nitrogen (Low): High to High	6			
Blood Urea Nitrogen (Low): Missing to Normal	47			
Blood Urea Nitrogen (Low): Missing to Low	11			
Blood Urea Nitrogen (Low): Missing to High	3			
Blood Urea Nitrogen (Low): Missing to Missing	39			
Calc Creatinine Clearance (High): Normal to Normal	540			
Calc Creatinine Clearance (High): Normal to Low	11			
Calc Creatinine Clearance (High): Normal to High	201			
Calc Creatinine Clearance(High): Normal to Missing	2			
Calc Creatinine Clearance (High): Low to Normal	166			

Calc Creatinine Clearance (High): Low to Low	107			
Calc Creatinine Clearance (High): Low to High	34			
Calc Creatinine Clearance (High): Low to Missing	1			
Calc Creatinine Clearance (High): High to Normal	13			
Calc Creatinine Clearance (High): High to High	101			
Calc Creatinine Clearance(High): Missing to Normal	46			
Calc Creatinine Clearance (High): Missing to Low	8			
Calc Creatinine Clearance (High): Missing to High	11			
Calc Creatinine Clearance(High):Missing to Missing	195			
Calc Creatinine Clearance (Low): Normal to Normal	393			
Calc Creatinine Clearance (Low): Normal to Low	353			
Calc Creatinine Clearance (Low): Normal to High	8			
Calc Creatinine Clearance (Low): Low to Normal	12			
Calc Creatinine Clearance (Low): Low to Low	294			
Calc Creatinine Clearance (Low): Low to High	1			
Calc Creatinine Clearance (Low): Low to Missing	1			
Calc Creatinine Clearance (Low): High to Normal	61			
Calc Creatinine Clearance (Low): High to Low	36			
Calc Creatinine Clearance (Low): High to High	17			
Calc Creatinine Clearance (Low): Missing to Normal	66			
Calc Creatinine Clearance (Low): Missing to Low	44			
Calc Creatinine Clearance (Low): Missing to High	17			
Calc Creatinine Clearance(Low): Missing to Missing	133			
Chloride (High): Normal to Normal	665			
Chloride (High): Normal to Low	2			
Chloride (High): Normal to High	508			
Chloride (High): Low to Normal	54			
Chloride (High): Low to High	13			
Chloride (High): High to Normal	4			
Chloride (High): High to High	58			
Chloride (High): Missing to Normal	41			
Chloride (High): Missing to High	32			
Chloride (High): Missing to Missing	59			
Chloride (Low): Normal to Normal	971			
Chloride (Low): Normal to Low	201			
Chloride (Low): Normal to High	3			

Chloride (Low): Low to Normal	31			
Chloride (Low): Low to Low	36			
Chloride (Low): High to Normal	57			
Chloride (Low): High to Low	4			
Chloride (Low): High to High	1			
Chloride (Low): Missing to Normal	60			
Chloride (Low): Missing to Low	13			
Chloride (Low): Missing to High	1			
Chloride (Low): Missing to Missing	58			
Lactate Dehydrogenase (High): Normal to Normal	328			
Lactate Dehydrogenase (High): Normal to High	499			
Lactate Dehydrogenase (High): Low to Normal	10			
Lactate Dehydrogenase (High): Low to Low	1			
Lactate Dehydrogenase (High): Low to High	4			
Lactate Dehydrogenase (High): High to Normal	74			
Lactate Dehydrogenase (High): High to High	449			
Lactate Dehydrogenase (High): Missing to Normal	16			
Lactate Dehydrogenase (High): Missing to High	30			
Lactate Dehydrogenase (High): Missing to Missing	25			
Lactate Dehydrogenase (Low): Normal to Normal	716			
Lactate Dehydrogenase (Low): Normal to Low	102			
Lactate Dehydrogenase (Low): Normal to High	9			
Lactate Dehydrogenase (Low): Low to Normal	5			
Lactate Dehydrogenase (Low): Low to Low	9			
Lactate Dehydrogenase (Low): Low to High	1			
Lactate Dehydrogenase (Low): High to Normal	426			
Lactate Dehydrogenase (Low): High to Low	31			
Lactate Dehydrogenase (Low): High to High	66			
Lactate Dehydrogenase (Low): Missing to Normal	39			
Lactate Dehydrogenase (Low): Missing to Low	3			
Lactate Dehydrogenase (Low): Missing to High	3			
Lactate Dehydrogenase (Low): Missing to Missing	26			
Total Protein (High): Normal to Normal	1091			
Total Protein (High): Normal to Low	20			
Total Protein (High): Normal to High	110			
Total Protein (High): Low to Normal	72			

Total Protein (High): Low to Low	14			
Total Protein (High): High to Normal	28			
Total Protein (High): High to High	24			
Total Protein (High): Missing to Normal	38			
Total Protein (High): Missing to Low	3			
Total Protein (High): Missing to High	4			
Total Protein (High): Missing to Missing	32			
Total Protein (Low): Normal to Normal	530			
Total Protein (Low): Normal to Low	691			
Total Protein (Low): Low to Normal	4			
Total Protein (Low): Low to Low	82			
Total Protein (Low): High to Normal	41			
Total Protein (Low): High to Low	11			
Total Protein (Low): Missing to Normal	23			
Total Protein (Low): Missing to Low	23			
Total Protein (Low): Missing to Missing	31			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival, as Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

End point title	Progression-Free Survival, as Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

End point type	Secondary

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Months				
median (confidence interval 95%)	20.67 (18.89 to 23.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Region of Enrollment: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by Region of Enrollment: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

End point type	Secondary

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Europe	Asia	North America	South America
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1009	177	34	121
Units: Months				
median (confidence interval 95%)	19.38 (17.51 to 21.75)	23.79 (15.90 to 28.85)	25.17 (14.42 to 29.44)	22.37 (17.51 to 32.72)

End point values	Africa	Other (Australia)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	24[30]		
Units: Months				
median (confidence interval 95%)	22.83 (12.02 to 27.86)	999999 (15.74 to 999999)		

Notes:

[30] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Age (≤65 vs. >65 Years): Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by Age (≤65 vs. >65 Years): Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

End point type	Secondary

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Age ≤65 Years	Age >65 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1167	269		
Units: Months				
median (confidence interval 95%)	21.98 (19.65 to 24.25)	14.72 (12.22 to 19.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by ECOG Performance Status at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by ECOG Performance Status at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

End point type	Secondary

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median

(full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	ECOG Performance Status 0 or 1	ECOG Performance Status 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1371	63		
Units: Months				
median (confidence interval 95%)	21.49 (19.45 to 23.98)	12.88 (8.67 to 15.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Taxane Chemotherapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by Taxane Chemotherapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

End point type	Secondary

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Docetaxel	Paclitaxel	Nab-Paclitaxel	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	775	588	65	
Units: Months				
median (confidence interval 95%)	19.38 (16.92 to 22.11)	23.23 (19.58 to 25.59)	19.22 (11.70 to 37.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Visceral Disease at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by Visceral Disease at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

End point type	Secondary

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Visceral Disease	Non-Visceral Disease		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	992	444		
Units: Months				
median (confidence interval 95%)	18.23 (16.13 to 20.57)	27.24 (23.75 to 34.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

End point type	Secondary

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Prior (Neo)Adjuvant Chemotherapy	No Prior (Neo)Adjuvant Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	786	650		
Units: Months				
median (confidence interval 95%)	19.12 (16.59 to 21.49)	23.49 (20.57 to 25.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Hormone Receptor Status at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by Hormone Receptor Status at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

End point type	Secondary

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Hormone Receptor Positive	Hormone Receptor Negative	Hormone Receptor Status Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	918	512	6	
Units: Months				
median (confidence interval 95%)	20.60 (18.53 to 23.82)	20.73 (17.05 to 23.79)	32.13 (11.63 to 61.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Previous Trastuzumab Therapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by Previous Trastuzumab Therapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

End point type	Secondary

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Previous Trastuzumab Therapy	No Previous Trastuzumab Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	400	1036		
Units: Months				
median (confidence interval 95%)	15.38 (13.67 to 19.02)	23.39 (20.67 to 25.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

End point type	Secondary

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1436			
Units: Months				
median (confidence interval 95%)	65.31 (60.88 to 70.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Region of Enrollment: Overall Survival

End point title	Subgroup Analysis by Region of Enrollment: Overall Survival

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

End point type	Secondary

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Europe	Asia	North America	South America
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1009	177[31]	34[32]	121[33]
Units: Months				
median (confidence interval 95%)	66.56 (61.90 to 73.49)	63.57 (47.57 to 999999)	55.56 (41.49 to 999999)	999999 (49.84 to 999999)

Notes:

[31] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

[32] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

[33] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

End point values	Africa	Other (Australia)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	24[34]		
Units: Months				
median (confidence interval 95%)	53.22 (33.35 to 63.87)	999999 (44.16 to 999999)		

Notes:

[34] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Age (≤65 vs. >65 Years): Overall Survival

End point title	Subgroup Analysis by Age (≤65 vs. >65 Years): Overall Survival

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

End point type	Secondary

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Age ≤65 Years	Age >65 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1167	269		
Units: Months				
median (confidence interval 95%)	70.01 (64.33 to 81.08)	50.10 (41.26 to 53.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by ECOG Performance Status at Baseline: Overall Survival

End point title	Subgroup Analysis by ECOG Performance Status at Baseline: Overall Survival

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

End point type	Secondary

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was

68.73 (0.03-87.29) months.

End point values	ECOG Performance Status 0 or 1	ECOG Performance Status 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1371	63		
Units: Months				
median (confidence interval 95%)	67.25 (63.44 to 76.52)	31.15 (20.50 to 39.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Taxane Chemotherapy: Overall Survival

End point title	Subgroup Analysis by Taxane Chemotherapy: Overall Survival

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

End point type	Secondary

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Docetaxel	Paclitaxel	Nab-Paclitaxel	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	775	588	65[35]	
Units: Months				
median (confidence interval 95%)	66.53 (61.67 to 77.27)	64.03 (56.61 to 72.25)	70.87 (39.69 to 999999)	

Notes:

[35] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Visceral Disease at Baseline: Overall Survival

End point title	Subgroup Analysis by Visceral Disease at Baseline: Overall Survival

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

End point type	Secondary

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Visceral Disease	Non-Visceral Disease		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	992	444[36]		
Units: Months				
median (confidence interval 95%)	57.10 (52.40 to 63.44)	81.08 (71.66 to 999999)		

Notes:

[36] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Overall Survival

End point title	Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Overall Survival

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

End point type	Secondary

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Prior (Neo)Adjuvant Chemotherapy	No Prior (Neo)Adjuvant Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	786	650[37]		
Units: Months				
median (confidence interval 95%)	57.10 (51.06 to 62.82)	79.80 (71.79 to 999999)		

Notes:

[37] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Hormone Receptor Status at Baseline: Overall Survival

End point title	Subgroup Analysis by Hormone Receptor Status at Baseline: Overall Survival

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

End point type	Secondary

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Hormone Receptor Positive	Hormone Receptor Negative	Hormone Receptor Status Unknown	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	918	512	6[38]	
Units: Months				
median (confidence interval 95%)	66.66 (62.39 to 77.27)	60.19 (52.34 to 67.71)	999999 (16.13 to 999999)	

Notes:

[38] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Previous Trastuzumab Therapy: Overall Survival

End point title	Subgroup Analysis by Previous Trastuzumab Therapy: Overall Survival

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

End point type	Secondary

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Previous Trastuzumab Therapy	No Previous Trastuzumab Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	400	1036[39]		
Units: Months				
median (confidence interval 95%)	54.08 (48.66 to 60.75)	73.50 (65.61 to 999999)		

Notes:

[39] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1

End point title	Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1

End point description:

The overall response rate was defined as the percentage of participants with complete response (CR) or partial response (PR) as their best confirmed response (≥4 weeks later), as assessed by the investigator using RECIST v1.1 from the start of study treatment until disease progression/recurrence or death. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Participants without post-baseline tumor assessments were considered non-responders.

End point type	Secondary

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression or death. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1198			
Units: Percentage of participants				
number (confidence interval 95%)	79.5 (77.07 to 81.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Best Overall Response as Assessed by the Investigator Using RECIST v1.1

End point title	Percentage of Participants by Best Overall Response as Assessed by the Investigator Using RECIST v1.1

End point description:

Best overall response (BOR) was defined as the best response recorded from the first dose of study treatment until disease progression/recurrence or death in the absence of disease progression. The hierarchy used to determine BOR: Complete Response (CR)>Partial Response (PR)>Stable Disease (SD)>Progressive Disease (PD)>Not Evaluable. Note that CR or PR was confirmed ≥4 weeks later. RECIST v1.1 responses are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum.; PD = At least 20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study, and absolute increase of ≥5 mm.; SD = Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on

End point type	Secondary

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression or death. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1198[40]			
Units: Percentage of participants				
number (not applicable)				
Complete Response (Confirmed)	14.6			
Partial Response (Confirmed)	64.9			
Stable Disease	15.3			
Progressive Disease	4.2			
Not Evaluable	1.1			

Notes:

[40] - Only includes subjects with measurable disease at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Age (≤65 vs. >65 Years): Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by Age (≤65 vs. >65 Years): Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1

End point description:

The overall response rate was defined as the percentage of participants with complete response (CR) or partial response (PR) as their best confirmed response (≥4 weeks later), as assessed by the investigator

using RECIST v1.1 from the start of study treatment until disease progression/recurrence or death. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Participants without post-baseline tumor assessments were considered non-responders.

End point type	Secondary

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression or death. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Age ≤65 Years	Age >65 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	968[41]	230[42]		
Units: Percentage of participants				
number (confidence interval 95%)	81.7 (79.13 to 84.10)	70.0 (63.63 to 75.85)		

Notes:

[41] - Only includes subjects with measurable disease at baseline.

[42] - Only includes subjects with measurable disease at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Subgroup Analysis by Taxane Chemotherapy: Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1

End point title	Subgroup Analysis by Taxane Chemotherapy: Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1

End point description:

The overall response rate was defined as the percentage of participants with complete response (CR) or partial response (PR) as their best confirmed response (≥4 weeks later), as assessed by the investigator using RECIST v1.1 from the start of study treatment until disease progression/recurrence or death. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Participants without post-baseline tumor assessments were considered non-responders.

End point type	Secondary

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression or death. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Docetaxel	Paclitaxel	Nab-Paclitaxel	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	657[43]	481[44]	53[45]	
Units: Percentage of participants				
number (confidence interval 95%)	78.4 (75.04 to 81.48)	82.1 (78.40 to 85.44)	77.4 (63.79 to 87.72)	

Notes:

[43] - Only includes subjects with measurable disease at baseline and those who had received any taxane.
[44] - Only includes subjects with measurable disease at baseline and those who had received any taxane.
[45] - Only includes subjects with measurable disease at baseline and those who had received any taxane.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CR or PR, or SD for at Least 6 Months) Based on Best Overall Response as Assessed by the Investigator Using RECIST v.1.1

End point title	Clinical Benefit Rate (CR or PR, or SD for at Least 6 Months) Based on Best Overall Response as Assessed by the Investigator Using RECIST v.1.1

End point description:

The clinical benefit rate was defined as the percentage of participants whose best confirmed response (≥4 weeks later) was a complete response (CR) or partial response (PR), or stable disease (SD) that lasted at least 6 months, as assessed by the investigator using RECIST v1.1 from the start of study treatment until disease progression/recurrence or death. Clinical benefit responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.; SD = Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD; at least 20% increase in sum of diameters of target lesions and absolute increase of ≥5 mm), taking as reference the smallest sum diameters while on study.

End point type	Secondary

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1198[46]			
Units: Percentage of participants				
number (confidence interval 95%)	86.2 (84.14 to 88.13)			

Notes:

[46] - Only includes subjects with measurable disease at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response as Assessed by the Investigator Using RECIST v1.1

End point title	Duration of Response as Assessed by the Investigator Using RECIST v1.1

End point description:

Duration of response (DOR) was defined as the time from when a confirmed best overall response of complete response (CR) or partial response (PR) was first documented to first documented disease progression or death from any cause (whichever occurred first). DOR was analyzed using a Kaplan-Meier approach. Participants who had not progressed or died after having had a confirmed response were censored at the date of their last tumor measurement. Response was assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter until event occurrence or end of study. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From date of first confirmed response (CR or PR) to first documented disease progression or death from any cause, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	952[47]			
Units: Months				
median (confidence interval 95%)	20.01 (18.20 to 22.21)			

Notes:

[47] - Only includes subjects with measurable disease at baseline and a documented confirmed response.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response for Participants with Best Overall Response of Complete Response or Partial Response, as Assessed by the Investigator Using RECIST v1.1

End point title	Time to Response for Participants with Best Overall Response of Complete Response or Partial Response, as Assessed by the Investigator Using RECIST v1.1

End point description:

Time to response (TTR) was defined as the time from the first study treatment administration to the date of first confirmed response (CR or PR). TTR was analyzed using a Kaplan-Meier approach. Participants who did not have CR or PR were censored at the date of their last evaluable tumor assessment. Participants for whom no post-baseline tumor assessments were available were censored at Day 1. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

From date of first study treatment until date of first confirmed response (CR or PR). The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1198			
Units: Months				
median (confidence interval 95%)	2.464 (2.398 to 2.497)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Cancer Therapy - Breast Cancer (FACT-B) Questionnaire Total Score Over the Course of the Study

End point title	Change from Baseline in Functional Assessment of Cancer Therapy - Breast Cancer (FACT-B) Questionnaire Total Score Over the Course of the Study

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. Participants were given a series of statements in each subscale and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B total score, ranging from 0 to 148, was the sum of the scores for each subscale, provided that at least 80% of the items had been answered; a higher score indicated a better quality of life. If any of the 5 subscale scores were missing, the total score was also set to missing. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

End point type	Secondary

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1429			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Absolute Value at Visit (n = 1306)	99.87 (± 20.548)			
Change from BL at Cycle 3 (n = 1158)	0.40 (± 15.526)			
Change from BL at Cycle 6 (n = 1089)	-1.93 (± 17.611)			
Change from BL at Cycle 9 (n = 1006)	0.87 (± 17.211)			

Change from BL at Cycle 12 (n = 891)	3.03 (± 17.426)			
Change from BL at Cycle 15 (n = 794)	3.33 (± 18.764)			
Change from BL at Cycle 18 (n = 718)	3.80 (± 18.689)			
Change from BL at Cycle 21 (n = 615)	4.06 (± 18.175)			
Change from BL at Cycle 24 (n = 570)	3.59 (± 19.570)			
Change from BL at Cycle 27 (n = 512)	3.14 (± 20.311)			
Change from BL at Cycle 30 (n = 515)	3.75 (± 18.877)			
Change from BL at Cycle 33 (n = 468)	3.58 (± 20.586)			
Change from BL at Cycle 36 (n = 427)	3.16 (± 18.838)			
Change from BL at Cycle 39 (n = 419)	1.66 (± 19.791)			
Change from BL at Cycle 42 (n = 385)	2.08 (± 20.658)			
Change from BL at Cycle 45 (n = 361)	2.22 (± 20.811)			
Change from BL at Cycle 48 (n = 340)	1.51 (± 21.268)			
Change from BL at Cycle 51 (n = 308)	1.95 (± 20.221)			
Change from BL at Cycle 54 (n = 282)	0.52 (± 20.784)			
Change from BL at Cycle 57 (n = 286)	0.54 (± 20.014)			
Change from BL at Cycle 60 (n = 262)	0.20 (± 21.207)			
Change from BL at Cycle 63 (n = 268)	0.61 (± 21.475)			
Change from BL at Cycle 66 (n = 241)	0.44 (± 20.633)			
Change from BL at Cycle 69 (n = 236)	-0.75 (± 21.419)			
Change from BL at Cycle 72 (n = 219)	-1.16 (± 21.951)			
Change from BL at Cycle 75 (n = 213)	-1.14 (± 21.132)			
Change from BL at Cycle 78 (n = 207)	0.11 (± 20.807)			
Change from BL at Cycle 81 (n = 192)	-1.03 (± 20.526)			
Change from BL at Cycle 84 (n = 181)	-1.67 (± 21.030)			
Change from BL at Cycle 87 (n = 174)	0.62 (± 21.183)			
Change from BL at Cycle 90 (n = 147)	0.00 (± 22.289)			
Change from BL at Cycle 93 (n = 129)	0.99 (± 21.474)			
Change from BL at Cycle 96 (n = 106)	2.36 (± 21.636)			
Change from BL at Cycle 99 (n = 85)	1.36 (± 23.195)			
Change from BL at Cycle 102 (n = 69)	1.20 (± 21.262)			

Change from BL at Cycle 105 (n = 55)	3.13 (± 20.385)			
Change from BL at Cycle 108 (n = 44)	2.22 (± 23.617)			
Change from BL at Cycle 111 (n = 36)	-0.48 (± 22.585)			
Change from BL at Cycle 114 (n = 19)	-4.42 (± 22.323)			
Change from BL at Cycle 117 (n = 11)	-4.96 (± 16.232)			
Change from BL at Cycle 120 (n = 4)	-8.64 (± 13.187)			
Change from BL at Cycle 123 (n = 2)	-20.94 (± 2.357)			
Change from BL at End of Treatment (n = 454)	-1.06 (± 19.923)			
Change from BL at Day 28 of Follow-Up (n = 568)	-1.96 (± 21.201)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACT-B Questionnaire Physical Well-Being Subscale Score Over the Course of the Study

End point title	Change from Baseline in FACT-B Questionnaire Physical Well-Being Subscale Score Over the Course of the Study

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the physical well-being subscale, participants were given a series of 7 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B physical well-being subscale score, ranging from 0 to 28, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

End point type	Secondary

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1429			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Absolute Value at Visit (n = 1331)	20.98 (± 6.044)			
Change from BL at Cycle 3 (n = 1193)	-1.13 (± 5.557)			

Change from BL at Cycle 6 (n = 1127)	-1.61 (± 5.994)			
Change from BL at Cycle 9 (n = 1033)	-0.31 (± 5.604)			
Change from BL at Cycle 12 (n = 919)	0.51 (± 5.599)			
Change from BL at Cycle 15 (n = 816)	0.51 (± 5.652)			
Change from BL at Cycle 18 (n = 734)	0.69 (± 5.543)			
Change from BL at Cycle 21 (n = 631)	0.73 (± 5.616)			
Change from BL at Cycle 24 (n = 581)	0.61 (± 5.690)			
Change from BL at Cycle 27 (n = 526)	0.47 (± 5.761)			
Change from BL at Cycle 30 (n = 523)	0.71 (± 5.584)			
Change from BL at Cycle 33 (n = 483)	0.56 (± 5.894)			
Change from BL at Cycle 36 (n = 437)	0.39 (± 5.512)			
Change from BL at Cycle 39 (n = 429)	-0.04 (± 5.647)			
Change from BL at Cycle 42 (n = 396)	0.22 (± 5.604)			
Change from BL at Cycle 45 (n = 370)	0.09 (± 5.698)			
Change from BL at Cycle 48 (n = 346)	0.11 (± 5.564)			
Change from BL at Cycle 51 (n = 319)	0.22 (± 5.280)			
Change from BL at Cycle 54 (n = 292)	-0.26 (± 5.765)			
Change from BL at Cycle 57 (n = 296)	-0.35 (± 5.695)			
Change from BL at Cycle 60 (n = 269)	-0.10 (± 5.630)			
Change from BL at Cycle 63 (n = 275)	-0.20 (± 5.696)			
Change from BL at Cycle 66 (n = 246)	0.29 (± 5.338)			
Change from BL at Cycle 69 (n = 243)	-0.60 (± 5.579)			
Change from BL at Cycle 72 (n = 224)	-0.35 (± 5.494)			
Change from BL at Cycle 75 (n = 218)	-0.72 (± 5.507)			
Change from BL at Cycle 78 (n = 213)	-0.44 (± 5.379)			
Change from BL at Cycle 81 (n = 197)	-0.65 (± 5.029)			
Change from BL at Cycle 84 (n = 186)	-0.81 (± 5.249)			
Change from BL at Cycle 87 (n = 181)	-0.36 (± 5.391)			
Change from BL at Cycle 90 (n = 153)	-0.66 (± 5.332)			
Change from BL at Cycle 93 (n = 134)	-0.42 (± 5.788)			
Change from BL at Cycle 96 (n = 110)	-0.28 (± 5.178)			
Change from BL at Cycle 99 (n = 88)	-0.21 (± 5.474)			
Change from BL at Cycle 102 (n = 72)	-0.80 (± 5.269)			
Change from BL at Cycle 105 (n = 57)	-0.07 (± 5.133)			
Change from BL at Cycle 108 (n = 45)	0.07 (± 5.775)			
Change from BL at Cycle 111 (n = 37)	0.38 (± 5.309)			
Change from BL at Cycle 114 (n = 20)	-1.70 (± 4.950)			

Change from BL at Cycle 117 (n = 12)	-1.83 (± 3.474)			
Change from BL at Cycle 120 (n = 4)	-2.38 (± 3.092)			
Change from BL at Cycle 123 (n = 2)	-5.58 (± 2.946)			
Change from BL at End of Treatment (n = 465)	-0.73 (± 6.366)			
Change from BL at Day 28 of Follow-Up (n = 583)	-0.95 (± 6.393)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACT-B Questionnaire Social Well-Being Subscale Score Over the Course of the Study

End point title	Change from Baseline in FACT-B Questionnaire Social Well-Being Subscale Score Over the Course of the Study

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the social well-being subscale, participants were given a series of 7 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B social well-being subscale score, ranging from 0 to 28, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

End point type	Secondary

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1429			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Absolute Value at Visit (n = 1329)	22.24 (± 4.993)			
Change from BL at Cycle 3 (n = 1189)	-0.41 (± 4.145)			
Change from BL at Cycle 6 (n = 1118)	-1.09 (± 4.320)			
Change from BL at Cycle 9 (n = 1032)	-1.02 (± 4.728)			
Change from BL at Cycle 12 (n = 921)	-1.19 (± 4.846)			
Change from BL at Cycle 15 (n = 812)	-1.28 (± 4.949)			

Change from BL at Cycle 18 (n = 733)	-1.19 (± 4.986)			
Change from BL at Cycle 21 (n = 630)	-1.24 (± 4.881)			
Change from BL at Cycle 24 (n = 580)	-1.26 (± 4.856)			
Change from BL at Cycle 27 (n = 525)	-1.48 (± 4.994)			
Change from BL at Cycle 30 (n = 523)	-1.18 (± 5.107)			
Change from BL at Cycle 33 (n = 482)	-1.45 (± 4.852)			
Change from BL at Cycle 36 (n = 437)	-1.54 (± 4.953)			
Change from BL at Cycle 39 (n = 430)	-1.77 (± 5.066)			
Change from BL at Cycle 42 (n = 394)	-1.73 (± 5.154)			
Change from BL at Cycle 45 (n = 370)	-1.50 (± 5.238)			
Change from BL at Cycle 48 (n = 345)	-1.84 (± 5.475)			
Change from BL at Cycle 51 (n = 318)	-2.01 (± 5.657)			
Change from BL at Cycle 54 (n = 293)	-1.77 (± 5.236)			
Change from BL at Cycle 57 (n = 297)	-1.88 (± 5.117)			
Change from BL at Cycle 60 (n = 270)	-2.01 (± 5.528)			
Change from BL at Cycle 63 (n = 277)	-2.18 (± 5.278)			
Change from BL at Cycle 66 (n = 246)	-2.19 (± 5.586)			
Change from BL at Cycle 69 (n = 243)	-2.24 (± 5.434)			
Change from BL at Cycle 72 (n = 224)	-2.49 (± 5.846)			
Change from BL at Cycle 75 (n = 219)	-2.40 (± 5.777)			
Change from BL at Cycle 78 (n = 213)	-2.33 (± 5.676)			
Change from BL at Cycle 81 (n = 197)	-2.53 (± 5.609)			
Change from BL at Cycle 84 (n = 187)	-2.96 (± 5.624)			
Change from BL at Cycle 87 (n = 181)	-2.29 (± 5.487)			
Change from BL at Cycle 90 (n = 152)	-2.38 (± 5.355)			
Change from BL at Cycle 93 (n = 134)	-1.97 (± 5.102)			
Change from BL at Cycle 96 (n = 110)	-1.94 (± 4.831)			
Change from BL at Cycle 99 (n = 89)	-2.07 (± 5.316)			
Change from BL at Cycle 102 (n = 73)	-1.70 (± 4.258)			
Change from BL at Cycle 105 (n = 58)	-1.76 (± 4.074)			
Change from BL at Cycle 108 (n = 46)	-1.75 (± 3.387)			

Change from BL at Cycle 111 (n = 38)	-1.94 (± 3.663)			
Change from BL at Cycle 114 (n = 20)	-2.31 (± 3.386)			
Change from BL at Cycle 117 (n = 12)	-1.83 (± 3.600)			
Change from BL at Cycle 120 (n = 4)	-2.85 (± 5.485)			
Change from BL at Cycle 123 (n = 2)	-1.92 (± 2.946)			
Change from BL at End of Treatment (n = 461)	-1.29 (± 4.911)			
Change from BL at Day 28 of Follow-Up (n = 581)	-1.61 (± 5.080)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACT-B Questionnaire Emotional Well-Being Subscale Score Over the Course of the Study

End point title	Change from Baseline in FACT-B Questionnaire Emotional Well-Being Subscale Score Over the Course of the Study

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the emotional well-being subscale, participants were given a series of 6 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B emotional well-being subscale score, ranging from 0 to 24, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

End point type	Secondary

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1429			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Absolute Value at Visit (n = 1333)	15.08 (± 4.990)			
Change from BL at Cycle 3 (n = 1194)	1.69 (± 4.219)			
Change from BL at Cycle 6 (n = 1124)	1.53 (± 4.526)			
Change from BL at Cycle 9 (n = 1032)	1.64 (± 4.624)			
Change from BL at Cycle 12 (n = 916)	2.02 (± 4.686)			
Change from BL at Cycle 15 (n = 811)	1.98 (± 4.778)			

Change from BL at Cycle 18 (n = 731)	2.03 (± 4.861)			
Change from BL at Cycle 21 (n = 628)	2.17 (± 4.877)			
Change from BL at Cycle 24 (n = 581)	2.19 (± 5.040)			
Change from BL at Cycle 27 (n = 523)	2.21 (± 5.171)			
Change from BL at Cycle 30 (n = 523)	2.17 (± 4.763)			
Change from BL at Cycle 33 (n = 478)	2.21 (± 5.275)			
Change from BL at Cycle 36 (n = 435)	2.32 (± 5.130)			
Change from BL at Cycle 39 (n = 430)	1.99 (± 5.115)			
Change from BL at Cycle 42 (n = 394)	1.96 (± 5.451)			
Change from BL at Cycle 45 (n = 367)	2.25 (± 5.367)			
Change from BL at Cycle 48 (n = 343)	1.82 (± 5.414)			
Change from BL at Cycle 51 (n = 317)	2.32 (± 5.311)			
Change from BL at Cycle 54 (n = 288)	1.84 (± 5.325)			
Change from BL at Cycle 57 (n = 293)	1.80 (± 5.256)			
Change from BL at Cycle 60 (n = 268)	1.59 (± 5.462)			
Change from BL at Cycle 63 (n = 274)	1.70 (± 5.336)			
Change from BL at Cycle 66 (n = 246)	1.52 (± 5.074)			
Change from BL at Cycle 69 (n = 243)	1.83 (± 5.351)			
Change from BL at Cycle 72 (n = 223)	1.56 (± 5.421)			
Change from BL at Cycle 75 (n = 217)	1.58 (± 5.308)			
Change from BL at Cycle 78 (n = 210)	1.72 (± 5.463)			
Change from BL at Cycle 81 (n = 196)	2.01 (± 5.750)			
Change from BL at Cycle 84 (n = 185)	2.06 (± 5.384)			
Change from BL at Cycle 87 (n = 180)	1.97 (± 5.558)			
Change from BL at Cycle 90 (n = 151)	2.08 (± 5.686)			
Change from BL at Cycle 93 (n = 134)	2.17 (± 5.388)			
Change from BL at Cycle 96 (n = 109)	2.40 (± 5.769)			
Change from BL at Cycle 99 (n = 88)	2.30 (± 6.041)			
Change from BL at Cycle 102 (n = 71)	2.07 (± 5.949)			
Change from BL at Cycle 105 (n = 58)	2.58 (± 5.902)			
Change from BL at Cycle 108 (n = 46)	2.34 (± 6.721)			
Change from BL at Cycle 111 (n = 38)	1.19 (± 7.241)			
Change from BL at Cycle 114 (n = 20)	1.55 (± 7.944)			
Change from BL at Cycle 117 (n = 12)	1.33 (± 4.185)			
Change from BL at Cycle 120 (n = 4)	0.75 (± 2.217)			
Change from BL at Cycle 123 (n = 2)	-0.50 (± 2.121)			
Change from BL at End of Treatment (n = 465)	0.30 (± 5.001)			
Change from BL at Day 28 of Follow-Up (n = 585)	0.37 (± 5.193)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACT-B Questionnaire Functional Well-Being Subscale Score Over the Course of the Study

End point title	Change from Baseline in FACT-B Questionnaire Functional Well-Being Subscale Score Over the Course of the Study

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the functional well-being subscale, participants were given a series of 7 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B functional well-being subscale score, ranging from 0 to 28, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

End point type	Secondary

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1429			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Absolute Value at Visit (n = 1335)	16.65 (± 6.096)			
Change from BL at Cycle 3 (n = 1192)	-0.47 (± 4.961)			
Change from BL at Cycle 6 (n = 1125)	-0.79 (± 5.437)			
Change from BL at Cycle 9 (n = 1032)	-0.11 (± 5.572)			
Change from BL at Cycle 12 (n = 915)	0.46 (± 5.577)			
Change from BL at Cycle 15 (n = 814)	0.78 (± 5.758)			
Change from BL at Cycle 18 (n = 732)	0.83 (± 5.797)			
Change from BL at Cycle 21 (n = 629)	0.89 (± 5.804)			
Change from BL at Cycle 24 (n = 583)	0.53 (± 5.903)			
Change from BL at Cycle 27 (n = 523)	0.71 (± 6.064)			
Change from BL at Cycle 30 (n = 524)	0.60 (± 5.961)			
Change from BL at Cycle 33 (n = 478)	0.67 (± 6.209)			
Change from BL at Cycle 36 (n = 436)	0.52 (± 5.687)			
Change from BL at Cycle 39 (n = 430)	0.26 (± 5.927)			
Change from BL at Cycle 42 (n = 393)	0.31 (± 6.038)			
Change from BL at Cycle 45 (n = 368)	0.34 (± 6.049)			
Change from BL at Cycle 48 (n = 344)	0.28 (± 6.227)			
Change from BL at Cycle 51 (n = 319)	0.23 (± 5.931)			
Change from BL at Cycle 54 (n = 289)	-0.06 (± 6.090)			
Change from BL at Cycle 57 (n = 294)	0.21 (± 5.925)			
Change from BL at Cycle 60 (n = 268)	0.01 (± 6.100)			
Change from BL at Cycle 63 (n = 275)	-0.06 (± 6.178)			
Change from BL at Cycle 66 (n = 247)	-0.07 (± 6.264)			
Change from BL at Cycle 69 (n = 243)	-0.47 (± 6.476)			

Change from BL at Cycle 72 (n = 224)	-0.50 (± 6.378)			
Change from BL at Cycle 75 (n = 217)	-0.40 (± 6.391)			
Change from BL at Cycle 78 (n = 211)	-0.18 (± 6.197)			
Change from BL at Cycle 81 (n = 197)	-0.29 (± 6.046)			
Change from BL at Cycle 84 (n = 186)	-0.48 (± 6.022)			
Change from BL at Cycle 87 (n = 180)	-0.08 (± 6.250)			
Change from BL at Cycle 90 (n = 152)	0.16 (± 6.587)			
Change from BL at Cycle 93 (n = 135)	0.58 (± 6.161)			
Change from BL at Cycle 96 (n = 111)	1.27 (± 6.663)			
Change from BL at Cycle 99 (n = 89)	0.46 (± 6.651)			
Change from BL at Cycle 102 (n = 73)	0.96 (± 6.327)			
Change from BL at Cycle 105 (n = 59)	1.14 (± 5.922)			
Change from BL at Cycle 108 (n = 46)	1.42 (± 6.902)			
Change from BL at Cycle 111 (n = 38)	0.32 (± 6.507)			
Change from BL at Cycle 114 (n = 20)	-0.25 (± 6.439)			
Change from BL at Cycle 117 (n = 12)	-0.58 (± 5.316)			
Change from BL at Cycle 120 (n = 4)	-2.00 (± 3.916)			
Change from BL at Cycle 123 (n = 2)	-5.00 (± 2.828)			
Change from BL at End of Treatment (n = 463)	-0.50 (± 6.132)			
Change from BL at Day 28 of Follow-Up (n = 586)	-0.70 (± 6.558)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACT-B Questionnaire Breast Cancer Subscale Score Over the Course of the Study

End point title	Change from Baseline in FACT-B Questionnaire Breast Cancer Subscale Score Over the Course of the Study

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the breast cancer subscale, participants were given a series of 10 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B breast cancer subscale score, ranging from 0 to 40, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

End point type	Secondary

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

End point values	Pertuzumab + Trastuzumab + Taxane			
Subject group type	Reporting group			
Number of subjects analysed	1429			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Absolute Value at Visit (n = 1326)	24.98 (± 6.296)			
Change from BL at Cycle 3 (n = 1181)	0.48 (± 5.101)			
Change from BL at Cycle 6 (n = 1117)	-0.11 (± 5.759)			
Change from BL at Cycle 9 (n = 1027)	0.52 (± 5.633)			
Change from BL at Cycle 12 (n = 910)	0.89 (± 5.770)			
Change from BL at Cycle 15 (n = 808)	1.16 (± 6.180)			
Change from BL at Cycle 18 (n = 729)	1.30 (± 6.043)			
Change from BL at Cycle 21 (n = 625)	1.30 (± 5.898)			
Change from BL at Cycle 24 (n = 580)	1.39 (± 6.231)			
Change from BL at Cycle 27 (n = 520)	1.17 (± 6.043)			
Change from BL at Cycle 30 (n = 521)	1.34 (± 5.968)			
Change from BL at Cycle 33 (n = 477)	1.34 (± 6.113)			
Change from BL at Cycle 36 (n = 435)	1.33 (± 6.030)			
Change from BL at Cycle 39 (n = 427)	1.12 (± 6.210)			
Change from BL at Cycle 42 (n = 393)	1.11 (± 6.499)			
Change from BL at Cycle 45 (n = 366)	1.13 (± 6.414)			
Change from BL at Cycle 48 (n = 343)	1.00 (± 6.679)			
Change from BL at Cycle 51 (n = 316)	0.99 (± 6.430)			
Change from BL at Cycle 54 (n = 291)	0.76 (± 6.555)			
Change from BL at Cycle 57 (n = 294)	0.70 (± 6.355)			
Change from BL at Cycle 60 (n = 267)	0.80 (± 6.586)			
Change from BL at Cycle 63 (n = 274)	1.32 (± 6.960)			
Change from BL at Cycle 66 (n = 246)	0.74 (± 6.822)			
Change from BL at Cycle 69 (n = 241)	0.54 (± 6.532)			
Change from BL at Cycle 72 (n = 223)	0.50 (± 7.142)			
Change from BL at Cycle 75 (n = 216)	0.85 (± 6.925)			
Change from BL at Cycle 78 (n = 210)	1.22 (± 6.899)			
Change from BL at Cycle 81 (n = 196)	0.27 (± 7.100)			
Change from BL at Cycle 84 (n = 184)	0.55 (± 6.690)			
Change from BL at Cycle 87 (n = 178)	1.17 (± 6.882)			
Change from BL at Cycle 90 (n = 150)	0.51 (± 7.313)			
Change from BL at Cycle 93 (n = 132)	0.30 (± 7.163)			
Change from BL at Cycle 96 (n = 110)	0.65 (± 6.240)			
Change from BL at Cycle 99 (n = 87)	1.19 (± 6.957)			
Change from BL at Cycle 102 (n = 72)	0.56 (± 6.189)			
Change from BL at Cycle 105 (n = 58)	0.68 (± 6.399)			
Change from BL at Cycle 108 (n = 45)	0.19 (± 6.982)			
Change from BL at Cycle 111 (n = 36)	0.01 (± 6.814)			
Change from BL at Cycle 114 (n = 19)	-1.67 (± 5.963)			

Change from BL at Cycle 117 (n = 11)	-1.56 (± 5.842)			
Change from BL at Cycle 120 (n = 4)	-2.17 (± 6.055)			
Change from BL at Cycle 123 (n = 2)	-7.94 (± 7.307)			
Change from BL at End of Treatment (n = 459)	0.88 (± 6.574)			
Change from BL at Day 28 of Follow-Up (n = 576)	0.66 (± 6.477)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until 28 days after last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Taxane

Reporting group description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

Serious adverse events	Pertuzumab + Trastuzumab + Taxane		
Total subjects affected by serious adverse events			
subjects affected / exposed	535 / 1436 (37.26%)		
number of deaths (all causes)	658		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
B-cell type acute leukemia			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast neoplasm			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchial carcinoma			

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cancer pain				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometrial cancer				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal stromal tumour				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lentigo maligna				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lobular breast carcinoma in situ				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastatic squamous cell carcinoma				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuroendocrine tumour of the lung				

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Papillary thyroid cancer				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal adenocarcinoma				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cancer				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thyroid cancer				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour embolism				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive crisis				
subjects affected / exposed	4 / 1436 (0.28%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				

subjects affected / exposed	3 / 1436 (0.21%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Circulatory collapse				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jugular vein thrombosis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphoedema				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subclavian vein thrombosis				

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Internal fixation of fracture			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Abortion			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	18 / 1436 (1.25%)		
occurrences causally related to treatment / all	7 / 21		
deaths causally related to treatment / all	0 / 0		
Asthenia			

subjects affected / exposed	6 / 1436 (0.42%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	5 / 1436 (0.35%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 3		
Fatigue			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mucosal inflammation			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Catheter site inflammation			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related thrombosis			

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug intolerance				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inflammatory pain				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza like illness				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion site extravasation				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nodule				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Drug hypersensitivity				

subjects affected / exposed	20 / 1436 (1.39%)			
occurrences causally related to treatment / all	4 / 20			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	5 / 1436 (0.35%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Breast haematoma				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine prolapse				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	16 / 1436 (1.11%)			
occurrences causally related to treatment / all	1 / 16			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	11 / 1436 (0.77%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	6 / 1436 (0.42%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			

Lung disorder			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aspiration			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cough			

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleuritic pain				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax spontaneous				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Agitation				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety disorder				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric decompensation			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device breakage			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device loosening			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Ejection fraction decreased			
subjects affected / exposed	18 / 1436 (1.25%)		
occurrences causally related to treatment / all	17 / 19		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	11 / 1436 (0.77%)		
occurrences causally related to treatment / all	10 / 18		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			

subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Computerised tomogram abdomen abnormal				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femur fracture				
subjects affected / exposed	8 / 1436 (0.56%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	8 / 1436 (0.56%)			
occurrences causally related to treatment / all	4 / 8			
deaths causally related to treatment / all	0 / 0			

Ankle fracture			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Carbon monoxide poisoning			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chemical burns of eye			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot fracture			

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fractured sacrum			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inflammation of wound			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb injury			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple fractures			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radiation injury				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulna fracture				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				

subjects affected / exposed	12 / 1436 (0.84%)			
occurrences causally related to treatment / all	12 / 13			
deaths causally related to treatment / all	1 / 1			
Atrial fibrillation				
subjects affected / exposed	8 / 1436 (0.56%)			
occurrences causally related to treatment / all	4 / 10			
deaths causally related to treatment / all	0 / 0			
Atrial thrombosis				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Cardiac failure congestive				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Left ventricular dysfunction				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure chronic				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac tamponade				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiovascular insufficiency				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracardiac mass				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mitral valve disease				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Right ventricular failure				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Sinus node dysfunction				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ischaemic stroke				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Seizure				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aphasia				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ataxia				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cauda equina syndrome				

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular disorder			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Hypoaesthesia			

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropsychiatric lupus			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Progressive supranuclear palsy			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Restless legs syndrome			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient global amnesia				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transverse sinus thrombosis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Trigeminal neuralgia				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	71 / 1436 (4.94%)			
occurrences causally related to treatment / all	21 / 75			
deaths causally related to treatment / all	1 / 1			
Neutropenia				
subjects affected / exposed	47 / 1436 (3.27%)			
occurrences causally related to treatment / all	5 / 56			
deaths causally related to treatment / all	0 / 1			
Anaemia				
subjects affected / exposed	8 / 1436 (0.56%)			
occurrences causally related to treatment / all	2 / 8			
deaths causally related to treatment / all	0 / 0			
Leukopenia				

subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone marrow failure			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	36 / 1436 (2.51%)		
occurrences causally related to treatment / all	16 / 43		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	7 / 1436 (0.49%)			
occurrences causally related to treatment / all	2 / 8			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	4 / 1436 (0.28%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Rectal haemorrhage				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Crohn's disease				

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer perforation			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileal stenosis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine polyp			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal stenosis			

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis chronic				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Small intestinal obstruction				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	4 / 1436 (0.28%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis sclerosing				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholestasis				

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Hepatocellular injury			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Liver injury			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pemphigus			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin ulcer			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	7 / 1436 (0.49%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Cystitis haemorrhagic			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders			
Osteonecrosis of jaw			
subjects affected / exposed	7 / 1436 (0.49%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Arthritis			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal osteoarthritis			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture pain			

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	26 / 1436 (1.81%)			
occurrences causally related to treatment / all	4 / 30			
deaths causally related to treatment / all	0 / 4			
Cellulitis				

subjects affected / exposed	15 / 1436 (1.04%)		
occurrences causally related to treatment / all	4 / 19		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	15 / 1436 (1.04%)		
occurrences causally related to treatment / all	3 / 15		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	10 / 1436 (0.70%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	10 / 1436 (0.70%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 3		
Vascular device infection			
subjects affected / exposed	9 / 1436 (0.63%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	8 / 1436 (0.56%)		
occurrences causally related to treatment / all	1 / 9		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	7 / 1436 (0.49%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 1		
Erysipelas			
subjects affected / exposed	6 / 1436 (0.42%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			

subjects affected / exposed	6 / 1436 (0.42%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	5 / 1436 (0.35%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	5 / 1436 (0.35%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	4 / 1436 (0.28%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	3 / 1436 (0.21%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			

subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Extradural abscess			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenic infection			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	2 / 1436 (0.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abscess limb			

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial pyelonephritis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary sepsis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridial infection			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium colitis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysentery			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis infectious			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis bacterial			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis C			

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster disseminated			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine infection			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung abscess			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Necrotising fasciitis			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal candidiasis			

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Paronychia				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pharyngitis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural infection				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonal sepsis				

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyomyositis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Salmonellosis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sinusitis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis fungal				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				

subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varicella				
subjects affected / exposed	1 / 1436 (0.07%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	4 / 1436 (0.28%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	4 / 1436 (0.28%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	3 / 1436 (0.21%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hypophosphataemia				
subjects affected / exposed	3 / 1436 (0.21%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Hypokalaemia				
subjects affected / exposed	2 / 1436 (0.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gout				

subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 1436 (0.07%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pertuzumab + Trastuzumab + Taxane		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1394 / 1436 (97.08%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	152 / 1436 (10.58%)		
occurrences (all)	217		
Hot flush			
subjects affected / exposed	129 / 1436 (8.98%)		
occurrences (all)	165		
Lymphoedema			
subjects affected / exposed	98 / 1436 (6.82%)		
occurrences (all)	121		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	457 / 1436 (31.82%)		
occurrences (all)	829		
Asthenia			

subjects affected / exposed	426 / 1436 (29.67%)		
occurrences (all)	1123		
Mucosal inflammation			
subjects affected / exposed	287 / 1436 (19.99%)		
occurrences (all)	490		
Pyrexia			
subjects affected / exposed	258 / 1436 (17.97%)		
occurrences (all)	387		
Oedema peripheral			
subjects affected / exposed	257 / 1436 (17.90%)		
occurrences (all)	344		
Influenza like illness			
subjects affected / exposed	96 / 1436 (6.69%)		
occurrences (all)	136		
Pain			
subjects affected / exposed	81 / 1436 (5.64%)		
occurrences (all)	114		
Chills			
subjects affected / exposed	75 / 1436 (5.22%)		
occurrences (all)	84		
Chest pain			
subjects affected / exposed	74 / 1436 (5.15%)		
occurrences (all)	86		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	271 / 1436 (18.87%)		
occurrences (all)	410		
Epistaxis			
subjects affected / exposed	263 / 1436 (18.31%)		
occurrences (all)	360		
Dyspnoea			
subjects affected / exposed	195 / 1436 (13.58%)		
occurrences (all)	260		
Oropharyngeal pain			

subjects affected / exposed	124 / 1436 (8.64%)		
occurrences (all)	156		
Rhinorrhoea			
subjects affected / exposed	100 / 1436 (6.96%)		
occurrences (all)	135		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	157 / 1436 (10.93%)		
occurrences (all)	183		
Depression			
subjects affected / exposed	78 / 1436 (5.43%)		
occurrences (all)	94		
Anxiety			
subjects affected / exposed	75 / 1436 (5.22%)		
occurrences (all)	87		
Investigations			
Ejection fraction decreased			
subjects affected / exposed	157 / 1436 (10.93%)		
occurrences (all)	215		
Weight decreased			
subjects affected / exposed	98 / 1436 (6.82%)		
occurrences (all)	115		
Nervous system disorders			
Headache			
subjects affected / exposed	328 / 1436 (22.84%)		
occurrences (all)	542		
Neuropathy peripheral			
subjects affected / exposed	328 / 1436 (22.84%)		
occurrences (all)	537		
Paraesthesia			
subjects affected / exposed	221 / 1436 (15.39%)		
occurrences (all)	366		
Dizziness			
subjects affected / exposed	205 / 1436 (14.28%)		
occurrences (all)	271		

Dysgeusia			
subjects affected / exposed	141 / 1436 (9.82%)		
occurrences (all)	193		
Peripheral sensory neuropathy			
subjects affected / exposed	120 / 1436 (8.36%)		
occurrences (all)	158		
Taste disorder			
subjects affected / exposed	75 / 1436 (5.22%)		
occurrences (all)	92		
Neurotoxicity			
subjects affected / exposed	72 / 1436 (5.01%)		
occurrences (all)	118		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	312 / 1436 (21.73%)		
occurrences (all)	521		
Neutropenia			
subjects affected / exposed	222 / 1436 (15.46%)		
occurrences (all)	439		
Leukopenia			
subjects affected / exposed	84 / 1436 (5.85%)		
occurrences (all)	162		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	169 / 1436 (11.77%)		
occurrences (all)	220		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	974 / 1436 (67.83%)		
occurrences (all)	2753		
Nausea			
subjects affected / exposed	512 / 1436 (35.65%)		
occurrences (all)	918		
Vomiting			

subjects affected / exposed	340 / 1436 (23.68%)		
occurrences (all)	531		
Constipation			
subjects affected / exposed	235 / 1436 (16.36%)		
occurrences (all)	347		
Stomatitis			
subjects affected / exposed	210 / 1436 (14.62%)		
occurrences (all)	326		
Abdominal pain			
subjects affected / exposed	206 / 1436 (14.35%)		
occurrences (all)	314		
Abdominal pain upper			
subjects affected / exposed	149 / 1436 (10.38%)		
occurrences (all)	187		
Dyspepsia			
subjects affected / exposed	141 / 1436 (9.82%)		
occurrences (all)	170		
Haemorrhoids			
subjects affected / exposed	79 / 1436 (5.50%)		
occurrences (all)	92		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	693 / 1436 (48.26%)		
occurrences (all)	813		
Rash			
subjects affected / exposed	365 / 1436 (25.42%)		
occurrences (all)	596		
Pruritus			
subjects affected / exposed	292 / 1436 (20.33%)		
occurrences (all)	466		
Dry skin			
subjects affected / exposed	167 / 1436 (11.63%)		
occurrences (all)	208		
Nail disorder			

subjects affected / exposed	163 / 1436 (11.35%)		
occurrences (all)	197		
Erythema			
subjects affected / exposed	137 / 1436 (9.54%)		
occurrences (all)	183		
Onycholysis			
subjects affected / exposed	118 / 1436 (8.22%)		
occurrences (all)	179		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	75 / 1436 (5.22%)		
occurrences (all)	94		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	328 / 1436 (22.84%)		
occurrences (all)	550		
Myalgia			
subjects affected / exposed	284 / 1436 (19.78%)		
occurrences (all)	476		
Back pain			
subjects affected / exposed	220 / 1436 (15.32%)		
occurrences (all)	289		
Muscle spasms			
subjects affected / exposed	196 / 1436 (13.65%)		
occurrences (all)	292		
Pain in extremity			
subjects affected / exposed	195 / 1436 (13.58%)		
occurrences (all)	248		
Bone pain			
subjects affected / exposed	135 / 1436 (9.40%)		
occurrences (all)	185		
Musculoskeletal pain			
subjects affected / exposed	128 / 1436 (8.91%)		
occurrences (all)	157		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	183 / 1436 (12.74%) 309		
Urinary tract infection subjects affected / exposed occurrences (all)	180 / 1436 (12.53%) 294		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	164 / 1436 (11.42%) 269		
Influenza subjects affected / exposed occurrences (all)	110 / 1436 (7.66%) 155		
Conjunctivitis subjects affected / exposed occurrences (all)	99 / 1436 (6.89%) 125		
Rhinitis subjects affected / exposed occurrences (all)	93 / 1436 (6.48%) 117		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	274 / 1436 (19.08%) 447		
Hypokalaemia subjects affected / exposed occurrences (all)	76 / 1436 (5.29%) 122		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 January 2012	Version 2. Key changes included the following: • Change of inclusion criteria to allow inclusion of patients with a baseline LVEF of at least 50%. • Exclusion of patients with alkaline phosphatase levels > 2.5 × the ULN (> 5 × ULN in patients with liver metastases, or >10 × ULN in patients with bone metastases). • Update of background and rationale to include efficacy and safety data from CLEOPATRA. • Change the definition of time to response from the time from the date of randomization to the date of first CR or PR to the time from date of enrolment to date of first CR or PR. • Update of criteria for elevated liver function tests. • Update of safety analyses to include all enrolled patients.
30 August 2012	Version 3. Key changes included the following: • Redefinition of the end of study to 45 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first. • Inclusion of patients who, prior to study entry had received up to two lines of hormonal therapies for metastatic or locally recurrent disease, one of which may have been in combination with everolimus. • Inclusion of patients with central nervous system (CNS) metastases if they were stable in the 3 months prior to screening after receiving local therapy but without anti-HER2 therapy. • Reduction of the time from major surgery to randomization from 28 days to 14 days based on recommendation from the Steering Committee for the PERTAIN study. • Reduction in the time from receipt of intravenous (IV) antibiotics prior to randomization from 14 days to 7 days based on recommendation from the PERTAIN Steering Committee. • Increase of the flexibility in the timing and order of administration of study medications. • Increase of the number of interim analyses from 3 to 5 planned analyses. • Update of the study rationale to include the latest CLEOPATRA study OS results. • Extension of the interval duration for the scheduling of tumor assessments after 36 months. • Increase of the defined timeline for scheduling of tumor assessments (excluding electrocardiogram [ECG]) to within 7 days of the scheduled visit. • Removal of the requirement for HER2 status to be measured within 28 days of enrolment if a previous result is available. • Update of the timeframe for reporting of SAEs. • Update of the Schedule of Assessments (SoA) to increase the number of days within which visits could occur before/after scheduled treatment day from ±3 to ±7 days.
09 May 2014	Version 4. Key changes included the following: • Updated guidance on the recommended pregnancy follow-up for trastuzumab and pregnancy testing technique. • Update of the study background to include CLEOPATRA OS results and US approval for neoadjuvant treatment. • Addition of an annual review of safety data by the iDMC following completion of enrollment. • Change in timing of follow-up visits to approximately every 3 months. • Inclusion of analysis of adverse event of special interest (AESI) and description of baseline covariates to be explored for ORR assessment. • Update to permit radiotherapy of brain metastases.
20 November 2015	Version 5. Key changes included the following: • Extension of the follow-up period of the study from 45 months to at least 60 months after the last patient had been enrolled into the study or all patients in the study had withdrawn consent, or died, whichever occurred first. • Update of the definition for abnormal liver function test (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] elevations) SAEs.

21 November 2018	Version 6. Key changes included the following: • Reduction in the frequency of imaging procedures for response assessments in long-term responders from every six cycles (approximately 4.5 months) in patients who remained progression free after 36 months to at least every 12 cycles following discussions at the iDMC meeting on 28 June 2018. • Reduction in the frequency of iDMC meetings from annually to approximately once per year. • Update of the policy on post-trial access to pertuzumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported