Clinical trial results:
A Two-Part, Randomized Phase III, Double-Blind, Multicenter Trial Assessing The Efficacy And Safety of Pertuzumab In Combination With Standard Chemotherapy Vs. Placebo Plus Standard Chemotherapy In Women With Recurrent Platinum-Resistant Epithelial Ovarian Cancer And Low HER3 mRNA Expression

Summary

EudraCT number	2011-005975-17
Trial protocol	ES DE IT NL SE BE AT DK
Global end of trial date	09 June 2016

Results information

Result version number	v2 (current)
This version publication date	26 April 2017
First version publication date	19 October 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MO28113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01684878
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: PENELOPE

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1: Safety Run-in Phase -To determine the safety and tolerability of pertuzumab in combination with either topotecan or paclitaxel. Part 2: -To determine if pertuzumab plus chemotherapy is superior to placebo plus chemotherapy as measured by progression-free survival (PFS) assessed by a blinded IRC including malignant bowel obstruction (MBO)

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Spain: 72
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Italy: 33
Worldwide total number of subjects	206
EEA total number of subjects	206

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)	109
From 65 to 84 years	97
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 208 subjects were entered into the study, 52 subjects in Part 1, and 156 subjects in Part 2 of the study. Of these, 203 received treatment with pertuzumab or pertuzumab-placebo (50 subjects in Part 1 and 153 subjects in Part 2).

Period 1

Period 1 title	Part 1: Safety Run in Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Pertuzumab + Topotecan

Arm description:

Subjects received pertuzumab and topotecan in cycles of 3 weeks until progressive disease as per investigator’s assessment, unacceptable toxicity, withdrawal of consent, or death.

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

Dosage and administration details:

Subjects were administered topotecan at a dosage of 1.25 milligram per metre square (mg/m^2) as a 30-minute IV infusion daily on Days 1 to 5 every 3 weeks.

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

Dosage and administration details:

Subjects were administered pertuzumab 840 milligrams (mg) intravenous (IV) infusion on Day 1 of the first treatment cycle as a loading dose, followed by 420 mg on Day 1 of each subsequent 3 weekly cycle.

Arm title	Part 1: Pertuzumab + Paclitaxel

Arm description:

Subjects received pertuzumab and paclitaxel in cycles of 3 weeks until progressive disease as per investigator’s assessment, unacceptable toxicity, withdrawal of consent, or death.

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

Dosage and administration details:

Subjects were administered paclitaxel at a dosage of 80 mg/m^2 as 1-hour IV infusion on Days 1, 8 and 15 every 3 weeks.

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

Dosage and administration details:

Subjects were administered pertuzumab 840 mg IV infusion on Day 1 of the first treatment cycle as a loading dose, followed by 420 mg on Day 1 of each subsequent 3 weekly cycle.

Number of subjects in period 1[1]	Part 1: Pertuzumab + Topotecan	Part 1: Pertuzumab + Paclitaxel
Started	22	28
Completed	6	5
Not completed	16	23
Death	15	20
Subjects withdrawn consent	1	1
Lost to follow-up	-	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The baseline period reflects the safety run-in phase of the study.

Period 2

Period 2 title	Part 2: Randomised Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Part 2: Pertuzumab+Chemotherapy

Arm description:

Subjects received pertuzumab and chemotherapy (paclitaxel or topotecan or gemcitabine) in cycles of 3 weeks until progressive disease as per investigator’s assessment, unacceptable toxicity, withdrawal of consent, or death. Chemotherapy was administered as per investigator's discretion.

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

Dosage and administration details:

Subjects were administered pertuzumab 840 mg IV infusion on Day 1 of the first treatment cycle as a loading dose, followed by 420 mg on Day 1 of each subsequent 3 weekly cycle.

Investigational medicinal product name	Paclitaxel (Chemotherapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered paclitaxel at a dosage of 80 mg/m^2 as 1-hour IV infusion on Days 1, 8 and 15 every 3 weeks as per the directions in the summary of product characteristics (SmPC).

Investigational medicinal product name	Topotecan (chemotherapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered topotecan at a dosage of 1.25 mg/m^2 as a 30-minute IV infusion daily on Days 1 to 5 every 3 weeks as per the directions described in the SmPC.

Investigational medicinal product name	Gemcitabine (Chemotherapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered gemcitabine at a dosage of 1000 mg/m^2 IV infusion on Days 1 and 8 every 3 weeks as per the directions described in the SmPC.

Arm title	Part 2: Placebo+Chemotherapy

Arm description:

Subjects received pertuzumab-matching placebo and chemotherapy (paclitaxel or topotecan or gemcitabine) in cycles of 3 weeks until progressive disease as per investigator’s assessment, unacceptable toxicity, withdrawal of consent, or death. Chemotherapy was administered as per investigator's discretion.

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

Dosage and administration details:

Subjects were administered pertuzumab matching placebo IV infusion on Day 1 of each 3 weekly cycle.

Investigational medicinal product name	Paclitaxel (Chemotherapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered paclitaxel at a dosage of 80 mg/m^2 as 1-hour IV infusion on Days 1, 8 and 15 every 3 weeks as per the directions in the summary of product characteristics (SmPC).

Investigational medicinal product name	Topotecan (chemotherapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered topotecan at a dosage of 1.25 mg/m^2 as a 30-minute IV infusion daily on Days 1 to 5 every 3 weeks as per the directions described in the SmPC.

Investigational medicinal product name	Gemcitabine (Chemotherapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered gemcitabine at a dosage of 1000 mg/m^2 IV infusion on Days 1 and 8 every 3 weeks as per the directions described in the SmPC.

Number of subjects in period 2	Part 2: Pertuzumab+Chemotherapy	Part 2: Placebo+Chemotherapy
Started	78	78
Subject Randomised But Not Treated	1	2
Subject Mis-randomised	2	0
Completed	0	0
Not completed	78	78
Subject noncompliance	-	1
Subject withdrew consent	1	2
Alive at data-cut	13	7
Death	62	68
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Pertuzumab + Topotecan
Reporting group description:	
Subjects received pertuzumab and topotecan in cycles of 3 weeks until progressive disease as per investigator's assessment, unacceptable toxicity, withdrawal of consent, or death.	
Reporting group title	Part 1: Pertuzumab + Paclitaxel
Reporting group description:	
Subjects received pertuzumab and paclitaxel in cycles of 3 weeks until progressive disease as per investigator's assessment, unacceptable toxicity, withdrawal of consent, or death.	

Reporting group values	Part 1: Pertuzumab + Topotecan	Part 1: Pertuzumab + Paclitaxel	Total
Number of subjects	22	28	50
Age categorical Units: Subjects			
Less than or equal to (≤)65 years	15	17	32
Greater than (>)65 years	7	11	18
Gender categorical Units: Subjects			
Female	22	28	50
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Overall Subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
Part 1: all subjects enrolled and treated in Part 1 of the study ('as treated' analysis) and Part 2: intent-to-treat (ITT) population was defined as all randomized subjects in the group to which they were randomly assigned ('as randomized' analysis).	

Reporting group values	Overall Subjects		
Number of subjects	206		
Age categorical Units: Subjects			
Less than or equal to (≤)65 years	116		
Greater than (>)65 years	90		
Gender categorical Units: Subjects			
Female	206		
Male	0		

End points

End points reporting groups

Reporting group title	Part 1: Pertuzumab + Topotecan
Reporting group description:	
Subjects received pertuzumab and topotecan in cycles of 3 weeks until progressive disease as per investigator's assessment, unacceptable toxicity, withdrawal of consent, or death.	
Reporting group title	Part 1: Pertuzumab + Paclitaxel
Reporting group description:	
Subjects received pertuzumab and paclitaxel in cycles of 3 weeks until progressive disease as per investigator's assessment, unacceptable toxicity, withdrawal of consent, or death.	
Reporting group title	Part 2: Pertuzumab+Chemotherapy
Reporting group description:	
Subjects received pertuzumab and chemotherapy (paclitaxel or topotecan or gemcitabine) in cycles of 3 weeks until progressive disease as per investigator's assessment, unacceptable toxicity, withdrawal of consent, or death. Chemotherapy was administered as per investigator's discretion.	
Reporting group title	Part 2: Placebo+Chemotherapy
Reporting group description:	
Subjects received pertuzumab-matching placebo and chemotherapy (paclitaxel or topotecan or gemcitabine) in cycles of 3 weeks until progressive disease as per investigator's assessment, unacceptable toxicity, withdrawal of consent, or death. Chemotherapy was administered as per investigator's discretion.	
Subject analysis set title	Overall Subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
Part 1: all subjects enrolled and treated in Part 1 of the study ('as treated' analysis) and Part 2: intent-to-treat (ITT) population was defined as all randomized subjects in the group to which they were randomly assigned ('as randomized' analysis).	

Primary: Part 1: Percentage of Subjects With Adverse Events (AEs)

End point title	Part 1: Percentage of Subjects With Adverse Events (AEs)[1]
End point description:	
An AE can be any unfavorable and unintended sign (including an abnormality laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. All Treated population included all subjects enrolled and treated in Part 1 of the study ('as treated' analysis) and who had received at least 1 dose of pertuzumab or chemotherapy.	
End point type	Primary
End point timeframe:	
Approximately 28 months (assessed at screening, baseline until 28 days after the last dose of study treatment)	

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: Descriptive analysis only.

End point values	Part 1: Pertuzumab + Topotecan	Part 1: Pertuzumab + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	28		
Units: percentage of subjects				
number (not applicable)	95.5	100		

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Progression Free Survival (PFS) as Assessed by a Blinded Independent Review Committee (IRC) Including Malignant Bowel Obstruction (MBO)

End point title	Part 2: Progression Free Survival (PFS) as Assessed by a Blinded Independent Review Committee (IRC) Including Malignant Bowel Obstruction (MBO)

End point description:

PFS (IRC-Assessed) was defined as the time from randomisation into Part 2 of the trial until progressive disease (PD), MBO or death from any cause, whichever occurred first per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. PD could base on symptom deterioration or was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or the appearance of one or more new lesions and/or the unequivocal progression of existing non-target lesions. ITT population was defined as all randomised subjects in the group to which they were randomly assigned ('as randomised' analysis).

End point type	Primary

End point timeframe:

Approximately 44 months (assessed at screening and every 9 weeks from randomisation until disease progression)

End point values	Part 2: Pertuzumab+Chemotherapy	Part 2: Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: months				
median (confidence interval 95%)	4.27 (3.65 to 6.11)	2.74 (2.14 to 4.73)		

Statistical analyses

Statistical analysis title	PFS assessed by IRC including MBO

Statistical analysis description:

The stratified time-to-event analysis included the treatment group variable plus the following stratification factors: selected chemotherapy cohort (gemcitabine versus topotecan vs paclitaxel), previous anti-angiogenic therapy (yes versus no), and progression-free interval (PFI) since platinum therapy (< 3 months versus 3-6 months). A hazard ratio < 1 favored the pertuzumab + chemotherapy treatment arm.

Comparison groups	Part 2: Pertuzumab+Chemotherapy v Part 2: Placebo+Chemotherapy

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4983
Method	2 sided log-rank
Parameter estimate	Hazard Ratio (stratified)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.27

Secondary: Part 1- Objective Response Rate (ORR)

End point title	Part 1- Objective Response Rate (ORR)

End point description:

ORR was defined as the number of participants with best overall response (BOR) of complete response (CR) or partial response (PR) recorded from the start of treatment, until the end of treatment. BOR documented as confirmed CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<)10 millimetre (mm). PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. All Treated subjects with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Approximately 28 months (assessed at baseline and every 9 weeks from randomization until disease progression)

End point values	Part 1: Pertuzumab + Topotecan	Part 1: Pertuzumab + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	24		
Units: percentage of subjects				
number (not applicable)	14.3	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2- Objective Response Rate (ORR)

End point title	Part 2- Objective Response Rate (ORR)

End point description:

ORR was defined as the number of subjects with BOR of CR or PR recorded from the start of treatment, until the end of treatment. BOR documented as confirmed CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<)10 millimetre (mm). PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. ITT population with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Approximately 44 months (assessed at baseline and every 9 weeks from randomisation until disease progression)

End point values	Part 2: Pertuzumab+Chemotherapy	Part 2: Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	69		
Units: percentage of subjects				
number (confidence interval 95%)	14.8 (7 to 26.2)	8.7 (3.3 to 18)		

Statistical analyses

Statistical analysis title	Part 2: ORR

Statistical analysis description:

Approximate 95% CI for difference of 2 rates using Hauck-Anderson method.

Comparison groups	Part 2: Pertuzumab+Chemotherapy v Part 2: Placebo+Chemotherapy
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4102
Method	Fisher exact
Parameter estimate	Difference in response rate
Point estimate	6.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	18.3

Secondary: Part 1: PFS Assessed by the Investigator

End point title	Part 1: PFS Assessed by the Investigator

End point description:

PFS as assessed by Investigator was defined as the time from first dose of pertuzumab or chemotherapy in Part 1 of the trial, until disease progression according to RECIST version 1.1, symptomatic deterioration or death from any cause, whichever occurs first. PD could base on symptom deterioration or was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or the appearance of one or more new lesions and/or the unequivocal progression of existing non-target lesions. Subjects were censored at the last tumor assessment. Subjects who have no tumor assessments after baseline and who were still alive will be censored at 1 day. All Treated population included all subjects enrolled and treated in Part 1 of the study (‘as treated’ analysis) and who had received at least 1 dose of pertuzumab or chemotherapy.

End point type	Secondary

End point timeframe:

Approximately 28 months (assessed at screening and every 9 weeks from randomisation until disease progression)

End point values	Part 1: Pertuzumab + Topotecan	Part 1: Pertuzumab + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	28		
Units: months				
median (confidence interval 95%)	4.07 (1.94 to 6.08)	4.24 (3.45 to 6.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Progression-free Survival (PFS) Assessed by the Investigator

End point title	Part 2: Progression-free Survival (PFS) Assessed by the Investigator

End point description:

PFS (Investigator-assessed) is defined as the time from randomisation, until disease progression according to RECIST v1.1 including death or MBO, whichever occurs first. Censoring is based on the last tumor assessment. If no tumor assessment post baseline, then censoring is at day 1. PD could base on symptom deterioration or was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or the appearance of one or more new lesions and/or the unequivocal progression of existing non-target lesions. ITT Population included all randomised subjects in the group to which they were randomly assigned (‘as randomised’ analysis).

End point type	Secondary

End point timeframe:

Approximately 44 months (assessed at screening and every 9 weeks from randomisation until disease progression)

End point values	Part 2: Pertuzumab+Chemotherapy	Part 2: Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: months				
median (confidence interval 95%)	4.22 (3.25 to 5.22)	3.94 (2.63 to 4.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) of Core 30 (C30) Score

End point title	Part 2: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) of Core 30 (C30) Score

End point description:

EORTC QLQ-C30: included functional scales (physical, role, cognitive, emotional, and social), global health status, symptom scales (fatigue, pain, nausea/vomiting) and single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea and financial difficulties). Most questions used 4-point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale [1 'very poor' to 7 'Excellent']). Scores averaged, transformed to 0-100 scale; for functional scores, a higher score represents a better level of functioning. For symptom scale scores a higher level represents a more severe level of symptoms. ITT population included all randomised subjects in the group to which they were randomly assigned ('as randomised' analysis).

End point type	Secondary

End point timeframe:

Baseline (assessed at baseline and every 9 weeks from randomisation until disease progression)

End point values	Part 2: Pertuzumab+Chemotherapy	Part 2: Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: units on a scale				
arithmetic mean (standard deviation)				
Functional Scales: Physical (n=71, 74)	71.1 (± 22.77)	74.9 (± 20.85)		
Functional Scales: Role (n=70, 73)	68.6 (± 33.16)	69.4 (± 32.4)		
Functional Scales: Emotional (n=71, 73)	59.5 (± 24.03)	65.9 (± 23.42)		
Functional Scales: Cognitive (n=71, 73)	81.2 (± 25.34)	84.9 (± 20.25)		
Functional Scales: Social (n=71, 73)	70.7 (± 30.01)	68.3 (± 29.81)		
Symptomatic Scales: Fatigue (n=71, 74)	41.2 (± 28.75)	38.4 (± 27.77)		
Symptomatic Scales: Nausea and vomiting (n=72, 74)	10.4 (± 15.68)	12.4 (± 20.47)		
Symptomatic Scales: Pain (n=72, 74)	35.2 (± 31.34)	31.1 (± 29.24)		
Symptomatic Scales: Dyspnoea (n=68, 73)	22.5 (± 28.47)	21.5 (± 27.98)		
Symptomatic Scales: Insomnia (n=69, 74)	35.3 (± 31.25)	31.5 (± 31.16)		
Symptomatic Scales: Appetite loss (n=71, 73)	24.9 (± 30.19)	21 (± 26.36)		
Symptomatic Scales: Constipation (n=69, 72)	25.6 (± 32.41)	26.4 (± 32.59)		
Symptomatic Scales: Diarrhoea (n=69, 72)	14.5 (± 26.49)	14.4 (± 22.26)		
Symptomatic Scales:Financial difficulties(n=70,72)	17.6 (± 28.78)	13.4 (± 22.83)		
Global health status / QoL scale (n=71, 72)	54.1 (± 24.99)	61.1 (± 22.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects With Adverse Events (AEs)

End point title	Part 2: Percentage of Subjects With Adverse Events (AEs)

End point description:

An AE can be any unfavorable and unintended sign (including an abnormality laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety population included all subjects who had received at least 1 dose of pertuzumab, pertuzumab-placebo, or chemotherapy.

End point type	Secondary

End point timeframe:

Approximately 28 months (assessed at screening, baseline until 28 days after the last dose of study treatment)

End point values	Part 2: Pertuzumab+Chemotherapy	Part 2: Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	76		
Units: percentage of subjects				
number (not applicable)	98.7	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Overall Survival

End point title	Part 2: Overall Survival

End point description:

Overall survival was defined as the time from randomization into Part 2 of the trial until death from any cause.

End point type	Secondary

End point timeframe:

Approximately 44 months (assessed at screening and every 9 weeks from randomisation until disease progression)

End point values	Part 2: Pertuzumab+Chemotherapy	Part 2: Placebo+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	78		
Units: months				
median (confidence interval 95%)	10.18 (6.67 to 15.24)	8.36 (6.14 to 11.99)		

Statistical analyses

Statistical analysis title	Part 2: Overall Survival
Statistical analysis description:	
The stratified time-to-event analysis included the treatment group variable plus the following stratification factors: selected chemotherapy cohort (gemcitabine versus topotecan versus paclitaxel), previous angiogenic therapy (yes versus no) and PFI since platinum therapy (<3 months versus 3-6 months). A hazard ratio <1 favored the Pertuzumab + Chemotherapy treatment group.	
Comparison groups	Part 2: Pertuzumab+Chemotherapy v Part 2: Placebo+Chemotherapy
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.596
Method	2 sided log-rank
Parameter estimate	Hazard ratio (stratified)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.32

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 28 months (assessed at screening, baseline until 28 days after the last dose of study treatment)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Part 1: Pertuzumab + Topotecan

Reporting group description:

Subjects received pertuzumab and topotecan in cycles of 3 weeks until progressive disease as per investigator’s assessment, unacceptable toxicity, withdrawal of consent, or death.

Reporting group title	Part 1: Pertuzumab + Paclitaxel

Reporting group description:

Subjects received pertuzumab and paclitaxel in cycles of 3 weeks until progressive disease as per investigator’s assessment, unacceptable toxicity, withdrawal of consent, or death.

Reporting group title	Part 2: Pertuzumab+Chemotherapy

Reporting group description:

Subjects received pertuzumab and chemotherapy (paclitaxel or topotecan or gemcitabine) in cycles of 3 weeks until progressive disease as per investigator's assessment, unacceptable toxicity, withdrawal of consent, or death. Chemotherapy was administered as per investigators discretion.

Reporting group title	Part 2: Placebo+Chemotherapy

Reporting group description:

Subjects received pertuzumab matching placebo and chemotherapy (paclitaxel or topotecan or gemcitabine) in cycles of 3 weeks until progressive disease as per investigator's assessment, unacceptable toxicity, withdrawal of consent, or death. Chemotherapy was administered as per investigators discretion.

Serious adverse events	Part 1: Pertuzumab + Topotecan	Part 1: Pertuzumab + Paclitaxel	Part 2: Pertuzumab+Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 22 (40.91%)	11 / 28 (39.29%)	29 / 77 (37.66%)
number of deaths (all causes)	0	2	6
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian Cancer			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	3 / 77 (3.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Performance Status Decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Physical Health Deterioration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Not yet coded	Additional description: This adverse event was not coded at the time of the primary analysis. The preferred term will be reported when available at the final analysis.		
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal Fistula			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutrophil Count Decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet Count Decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Contrast Media Reaction			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral Neck Fracture			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Coronary Syndrome			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral Ischaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Neutropenia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	3 / 77 (3.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Marrow Failure			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Intestinal Obstruction			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	4 / 77 (5.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	3 / 77 (3.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	3 / 77 (3.90%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Lower			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain Upper			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Fissure			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Fistula			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eczema Asteatotic			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Disorder			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Obstruction			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Device Related Infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective Myositis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis Pneumococcal			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Abscess			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased Appetite			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Placebo+Chemotherapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 76 (43.42%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian Cancer			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Death			

subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Performance Status Decreased				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Asthenia				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General Physical Health Deterioration				
subjects affected / exposed	3 / 76 (3.95%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 1			
Not yet coded	Additional description: This adverse event was not coded at the time of the primary analysis. The preferred term will be reported when available at the final analysis.			
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Vaginal Fistula				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pleural Effusion				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutrophil Count Decreased			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet Count Decreased			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Weight Decreased			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Contrast Media Reaction			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral Neck Fracture			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Humerus Fracture			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Acute Myocardial Infarction				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acute Coronary Syndrome				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral Ischaemia				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hydrocephalus				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ischaemic Stroke				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pancytopenia				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile Neutropenia				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone Marrow Failure				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Intestinal Obstruction				
subjects affected / exposed	4 / 76 (5.26%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 2			
Abdominal Pain				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain Lower				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain Upper				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anal Fissure				
subjects affected / exposed	0 / 76 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal Fistula			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eczema Asteatotic			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Disorder			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Obstruction			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Abdominal Infection			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device Related Infection			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Infective Myositis			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Kidney Infection			

subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningitis Pneumococcal			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal Infection			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal Abscess			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Decreased Appetite			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 76 (1.32%)		
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	Part 1: Pertuzumab + Topotecan	Part 1: Pertuzumab + Paclitaxel	Part 2: Pertuzumab+Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)	27 / 28 (96.43%)	72 / 77 (93.51%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 22 (63.64%)	8 / 28 (28.57%)	32 / 77 (41.56%)
occurrences (all)	22	10	48
Fatigue			
subjects affected / exposed	5 / 22 (22.73%)	10 / 28 (35.71%)	21 / 77 (27.27%)
occurrences (all)	5	13	31
Pyrexia			
subjects affected / exposed	5 / 22 (22.73%)	5 / 28 (17.86%)	9 / 77 (11.69%)
occurrences (all)	7	5	14
Mucosal Inflammation			
subjects affected / exposed	7 / 22 (31.82%)	2 / 28 (7.14%)	11 / 77 (14.29%)
occurrences (all)	10	5	14
Oedema Peripheral			
subjects affected / exposed	5 / 22 (22.73%)	2 / 28 (7.14%)	12 / 77 (15.58%)
occurrences (all)	5	2	12
Influenza Like Illness			
subjects affected / exposed	3 / 22 (13.64%)	0 / 28 (0.00%)	4 / 77 (5.19%)
occurrences (all)	3	0	5
Malaise			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Oedema			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	5 / 22 (22.73%)	7 / 28 (25.00%)	16 / 77 (20.78%)
occurrences (all)	5	13	19
Cough			
subjects affected / exposed	5 / 22 (22.73%)	2 / 28 (7.14%)	7 / 77 (9.09%)
occurrences (all)	6	2	10
Dyspnoea			
subjects affected / exposed	3 / 22 (13.64%)	4 / 28 (14.29%)	7 / 77 (9.09%)
occurrences (all)	3	4	7
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 22 (0.00%)	3 / 28 (10.71%)	0 / 77 (0.00%)
occurrences (all)	0	5	0
Insomnia			
subjects affected / exposed	0 / 22 (0.00%)	3 / 28 (10.71%)	5 / 77 (6.49%)
occurrences (all)	0	5	6
Investigations			
Weight Decreased			
subjects affected / exposed	2 / 22 (9.09%)	2 / 28 (7.14%)	2 / 77 (2.60%)
occurrences (all)	2	2	2
Ejection Fraction Decreased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	3	0
Blood Creatinine Increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Platelet Count Decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	6 / 77 (7.79%)
occurrences (all)	0	0	10
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	3 / 77 (3.90%)
occurrences (all)	0	0	3
Aspartate Aminotransferase Increased			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	3 / 77 (3.90%)
occurrences (all)	0	0	4
Neutrophil Count Decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	7 / 77 (9.09%)
occurrences (all)	0	0	8
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	3 / 77 (3.90%)
occurrences (all)	0	0	3
White Blood Cell Count Decreased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	6 / 77 (7.79%)
occurrences (all)	0	0	6
Alanine aminotransferase increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	5 / 77 (6.49%)
occurrences (all)	0	0	6
Nervous system disorders			
Peripheral Sensory Neuropathy			
subjects affected / exposed	2 / 22 (9.09%)	7 / 28 (25.00%)	10 / 77 (12.99%)
occurrences (all)	2	7	10
Headache			
subjects affected / exposed	3 / 22 (13.64%)	1 / 28 (3.57%)	7 / 77 (9.09%)
occurrences (all)	3	1	9
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)	1 / 28 (3.57%)	7 / 77 (9.09%)
occurrences (all)	2	2	9
Neuropathy Peripheral			
subjects affected / exposed	1 / 22 (4.55%)	2 / 28 (7.14%)	7 / 77 (9.09%)
occurrences (all)	1	2	8
Paraesthesia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 28 (7.14%)	4 / 77 (5.19%)
occurrences (all)	1	7	6
Ageusia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Dysgeusia			

subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	9 / 77 (11.69%)
occurrences (all)	0	2	10
Peripheral Motor Neuropathy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 22 (68.18%)	10 / 28 (35.71%)	28 / 77 (36.36%)
occurrences (all)	27	13	43
Neutropenia			
subjects affected / exposed	5 / 22 (22.73%)	3 / 28 (10.71%)	23 / 77 (29.87%)
occurrences (all)	13	3	45
Thrombocytopenia			
subjects affected / exposed	3 / 22 (13.64%)	0 / 28 (0.00%)	3 / 77 (3.90%)
occurrences (all)	4	0	5
Leukopenia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 28 (7.14%)	4 / 77 (5.19%)
occurrences (all)	1	3	6
Thrombocytosis			
subjects affected / exposed	3 / 22 (13.64%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences (all)	3	0	0
Febrile Neutropenia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Vision Blurred			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 22 (63.64%)	22 / 28 (78.57%)	50 / 77 (64.94%)
occurrences (all)	34	52	110
Nausea			

subjects affected / exposed	11 / 22 (50.00%)	10 / 28 (35.71%)	31 / 77 (40.26%)
occurrences (all)	18	14	65
Vomiting			
subjects affected / exposed	13 / 22 (59.09%)	5 / 28 (17.86%)	19 / 77 (24.68%)
occurrences (all)	18	6	35
Abdominal Pain			
subjects affected / exposed	6 / 22 (27.27%)	4 / 28 (14.29%)	16 / 77 (20.78%)
occurrences (all)	6	4	26
Constipation			
subjects affected / exposed	5 / 22 (22.73%)	5 / 28 (17.86%)	12 / 77 (15.58%)
occurrences (all)	7	9	18
Stomatitis			
subjects affected / exposed	2 / 22 (9.09%)	5 / 28 (17.86%)	9 / 77 (11.69%)
occurrences (all)	2	7	9
Abdominal Pain Upper			
subjects affected / exposed	3 / 22 (13.64%)	1 / 28 (3.57%)	6 / 77 (7.79%)
occurrences (all)	3	1	7
Dyspepsia			
subjects affected / exposed	1 / 22 (4.55%)	3 / 28 (10.71%)	4 / 77 (5.19%)
occurrences (all)	1	4	5
Dry Mouth			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	2 / 77 (2.60%)
occurrences (all)	0	6	2
Rectal Haemorrhage			
subjects affected / exposed	2 / 22 (9.09%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Abdominal Distension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	8
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	6
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 22 (31.82%)	10 / 28 (35.71%)	15 / 77 (19.48%)
occurrences (all)	8	11	15

Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	0 / 22 (0.00%)	3 / 28 (10.71%)	4 / 77 (5.19%)
occurrences (all)	0	3	4
Nail Disorder			
subjects affected / exposed	0 / 22 (0.00%)	3 / 28 (10.71%)	5 / 77 (6.49%)
occurrences (all)	0	3	6
Rash			
subjects affected / exposed	1 / 22 (4.55%)	2 / 28 (7.14%)	7 / 77 (9.09%)
occurrences (all)	1	2	8
Dry Skin			
subjects affected / exposed	2 / 22 (9.09%)	0 / 28 (0.00%)	7 / 77 (9.09%)
occurrences (all)	2	0	7
Erythema			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Pain Of Skin			
subjects affected / exposed	2 / 22 (9.09%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Rash Maculo-Papular			
subjects affected / exposed	2 / 22 (9.09%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	5 / 77 (6.49%)
occurrences (all)	0	0	6
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 22 (4.55%)	6 / 28 (21.43%)	8 / 77 (10.39%)
occurrences (all)	1	7	10
Myalgia			
subjects affected / exposed	1 / 22 (4.55%)	4 / 28 (14.29%)	0 / 77 (0.00%)
occurrences (all)	1	5	0
Arthralgia			
subjects affected / exposed	0 / 22 (0.00%)	4 / 28 (14.29%)	4 / 77 (5.19%)
occurrences (all)	0	4	4
Muscle Spasms			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	6 / 77 (7.79%)
occurrences (all)	0	0	9
Musculoskeletal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Pain In Extremity			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 22 (9.09%)	2 / 28 (7.14%)	10 / 77 (12.99%)
occurrences (all)	2	4	11
Urinary Tract Infection			
subjects affected / exposed	3 / 22 (13.64%)	1 / 28 (3.57%)	7 / 77 (9.09%)
occurrences (all)	3	1	10
Nail Infection			
subjects affected / exposed	2 / 22 (9.09%)	0 / 28 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	5
Rhinitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	8
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	8 / 22 (36.36%)	5 / 28 (17.86%)	13 / 77 (16.88%)
occurrences (all)	10	7	18
Hypomagnesaemia			
subjects affected / exposed	3 / 22 (13.64%)	4 / 28 (14.29%)	7 / 77 (9.09%)
occurrences (all)	4	4	7
Hypokalaemia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 28 (7.14%)	9 / 77 (11.69%)
occurrences (all)	5	2	13
Hypoalbuminaemia			

subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Hyponatraemia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 28 (7.14%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Hypocalcaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	4

Non-serious adverse events	Part 2: Placebo+Chemotherapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 76 (98.68%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	24 / 76 (31.58%)		
occurrences (all)	32		
Fatigue			
subjects affected / exposed	24 / 76 (31.58%)		
occurrences (all)	30		
Pyrexia			
subjects affected / exposed	12 / 76 (15.79%)		
occurrences (all)	13		
Mucosal Inflammation			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	7		
Oedema Peripheral			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	9		
Influenza Like Illness			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences (all)	1		
Malaise			

subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Cough			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	12 / 76 (15.79%)		
occurrences (all)	12		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Investigations			
Weight Decreased			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Ejection Fraction Decreased			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Lymphocyte Count Decreased			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Blood Creatinine Increased			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Platelet Count Decreased			

subjects affected / exposed	2 / 76 (2.63%)		
occurrences (all)	3		
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Aspartate Aminotransferase Increased			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Neutrophil Count Decreased			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences (all)	4		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	8		
White Blood Cell Count Decreased			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	6		
Alanine aminotransferase increased			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	6		
Nervous system disorders			
Peripheral Sensory Neuropathy			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	10		
Headache			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	7		
Dizziness			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	5		
Neuropathy Peripheral			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	9		
Paraesthesia			

subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 8		
Ageusia subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0		
Dysgeusia subjects affected / exposed occurrences (all)	7 / 76 (9.21%) 7		
Peripheral Motor Neuropathy subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	32 / 76 (42.11%) 48		
Neutropenia subjects affected / exposed occurrences (all)	21 / 76 (27.63%) 36		
Thrombocytopenia subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 5		
Leukopenia subjects affected / exposed occurrences (all)	9 / 76 (11.84%) 20		
Thrombocytosis subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0		
Febrile Neutropenia subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 76 (0.00%) 0		
Eye disorders			

Vision Blurred			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	23 / 76 (30.26%)		
occurrences (all)	27		
Nausea			
subjects affected / exposed	34 / 76 (44.74%)		
occurrences (all)	53		
Vomiting			
subjects affected / exposed	23 / 76 (30.26%)		
occurrences (all)	35		
Abdominal Pain			
subjects affected / exposed	21 / 76 (27.63%)		
occurrences (all)	23		
Constipation			
subjects affected / exposed	22 / 76 (28.95%)		
occurrences (all)	24		
Stomatitis			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Abdominal Pain Upper			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	12		
Dyspepsia			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences (all)	3		
Dry Mouth			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	9		
Rectal Haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Abdominal Distension			

subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 76 (27.63%)		
occurrences (all)	21		
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Nail Disorder			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences (all)	3		
Dry Skin			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Pain Of Skin			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Rash Maculo-Papular			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Back Pain			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	11		
Myalgia			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Muscle Spasms			
subjects affected / exposed	3 / 76 (3.95%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Pain In Extremity			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	7		
Urinary Tract Infection			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	7		
Nail Infection			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

Decreased Appetite			
subjects affected / exposed	17 / 76 (22.37%)		
occurrences (all)	20		
Hypomagnesaemia			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	7		
Hypokalaemia			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	8		
Hypoalbuminaemia			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	0 / 76 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2013	1. The Phase of the study from Phase II to Phase III 2. Added that primary endpoint PFS is IRC-Assessed 3. Added PFS (Investigator-Assessed) as a secondary endpoint 4. Added a pharmacokinetic (PK) sub-study for subjects receiving topotecan in Part 2 of the study 5. Added analysis of the effect of anti-therapeutic antibodies (ATA) 6. The definition of the end of study and the length of the follow-up were modified 7. An efficacy interim analysis for OS was introduced for Part 2 of the study 8. Independent Review Committee was implemented

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported