



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 | |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 19 October 2016 |
| First version publication date | 19 October 2016 |

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 | Interim |
| Date of interim/final analysis | 30 January 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|------------------------------|----|
| Global end of trial reached? | 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? | No |
| 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 | 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.

| | |
|--|-----------------|
| 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/m²) as a 30-minute IV infusion daily on Days 1 to 5 every 3 weeks.

| | |
|------------------|---------------------------------|
| 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 | 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 |
| 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/m² as 1-hour IV infusion on Days 1, 8 and 15 every 3 weeks.

| Number of subjects in period 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 |

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/m² 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 ^[1] | 2 ^[2] |
| Subject Mis-randomised | 2 ^[3] | 0 ^[4] |
| Completed | 35 | 33 |
| Not completed | 43 | 45 |
| Death | 39 | 43 |
| Subjects withdrawn consent | 2 | 2 |
| Lost to follow-up | 2 | - |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone represents a characteristic of the randomisation of the intent-to-treat (ITT) population.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone represents a characteristic of the randomisation of the intent-to-treat (ITT) population.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone represents a characteristic of the randomisation of the intent-to-treat (ITT) population.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone represents a characteristic of the randomisation of the intent-to-treat (ITT) population.

Baseline characteristics

Reporting groups^[1]

| | |
|-----------------------|--------------------------------|
| 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.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial because the subjects in baseline period equals to the number of subjects enrolled for part 1 of study. The data for baseline characteristics has been reported for worldwide number of subjects by creating subject analysis set for 'Overall Subjects'.

| 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 (\leq)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 (\leq)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: The descriptive data was planned to be reported for the endpoint.

| 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 randomization 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 28 months (assessed at screening and every 9 weeks from randomization until disease progression)

| End point values | Part 2: Pertuzumab+C hemotherapy | Part 2: Placebo+Chem otherapy | | |
|----------------------------------|--|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 78 | 78 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.27 (3.65 to 6.01) | 2.63 (2.14 to 4.27) | | |

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 | = 0.1387 |
| Method | 2 sided log-rank |
| Parameter estimate | Hazard Ratio (stratified) |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.11 |

Secondary: Part 1- Objective Response Rate (ORR)

| | |
|------------------------|---|
| End point title | Part 1- Objective Response Rate (ORR) |
| End point description: | <p>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.</p> |
| End point type | Secondary |
| End point timeframe: | <p>Approximately 28 months (assessed at baseline and every 9 weeks from randomization until disease progression)</p> |

| 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: | <p>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.</p> |

| | |
|---|-----------|
| 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 2: Pertuzumab+C hemotherapy | Part 2: Placebo+Chem otherapy | | |
|----------------------------------|--|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 69 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 13.1 (5.8 to 24.2) | 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 | = 0.5723 |
| Method | Fisher exact |
| Parameter estimate | Difference in response rate |
| Point estimate | 4.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.25 |
| upper limit | 16.09 |

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

| End point values | Part 2: Pertuzumab+C hemotherapy | Part 2: Placebo+Chem otherapy | | |
|----------------------------------|--|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 78 | 78 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.14 (2.53 to 5.09) | 3.94 (2.63 to 4.3) | | |

Statistical analyses

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+C hemotherapy | Part 2: Placebo+Chem otherapy | | |
|---|--|-------------------------------------|--|--|
| 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+C hemotherapy | Part 2: Placebo+Chem otherapy | | |
|-------------------------------|--|-------------------------------------|--|--|
| 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

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+Chemo therapy |
|---|---|--|---|
| 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 occurrences (all) | 0 / 22 (0.00%) 0 | 2 / 28 (7.14%) 2 | 9 / 77 (11.69%) 10 |
| Peripheral Motor Neuropathy subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 28 (0.00%) 0 | 0 / 77 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 15 / 22 (68.18%) 27 | 10 / 28 (35.71%) 13 | 28 / 77 (36.36%) 43 |
| Neutropenia subjects affected / exposed occurrences (all) | 5 / 22 (22.73%) 13 | 3 / 28 (10.71%) 3 | 23 / 77 (29.87%) 45 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 4 | 0 / 28 (0.00%) 0 | 3 / 77 (3.90%) 5 |
| Leukopenia subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 2 / 28 (7.14%) 3 | 4 / 77 (5.19%) 6 |
| Thrombocytosis subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 3 | 0 / 28 (0.00%) 0 | 0 / 77 (0.00%) 0 |
| Febrile Neutropenia subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | 0 / 28 (0.00%) 0 | 0 / 77 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 2 / 28 (7.14%) 2 | 0 / 77 (0.00%) 0 |
| Eye disorders | | | |
| Vision Blurred subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 2 / 28 (7.14%) 2 | 0 / 77 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 14 / 22 (63.64%) 34 | 22 / 28 (78.57%) 52 | 50 / 77 (64.94%) 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 | 4 / 76 (5.26%) | | |
| occurrences (all) | 8 | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | | |
| occurrences (all) | 7 | | |
| Peripheral Motor Neuropathy | | | |
| subjects affected / exposed | 4 / 76 (5.26%) | | |
| occurrences (all) | 4 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 32 / 76 (42.11%) | | |
| occurrences (all) | 48 | | |
| Neutropenia | | | |
| subjects affected / exposed | 21 / 76 (27.63%) | | |
| occurrences (all) | 36 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | | |
| occurrences (all) | 5 | | |
| Leukopenia | | | |
| subjects affected / exposed | 9 / 76 (11.84%) | | |
| occurrences (all) | 20 | | |
| Thrombocytosis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | | |
| occurrences (all) | 0 | | |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |

| | | | |
|--|------------------------|--|--|
| Vision Blurred subjects affected / exposed occurrences (all) | 0 / 76 (0.00%) 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 23 / 76 (30.26%) 27 | | |
| Nausea subjects affected / exposed occurrences (all) | 34 / 76 (44.74%) 53 | | |
| Vomiting subjects affected / exposed occurrences (all) | 23 / 76 (30.26%) 35 | | |
| Abdominal Pain subjects affected / exposed occurrences (all) | 21 / 76 (27.63%) 23 | | |
| Constipation subjects affected / exposed occurrences (all) | 22 / 76 (28.95%) 24 | | |
| Stomatitis subjects affected / exposed occurrences (all) | 5 / 76 (6.58%) 5 | | |
| Abdominal Pain Upper subjects affected / exposed occurrences (all) | 9 / 76 (11.84%) 12 | | |
| Dyspepsia subjects affected / exposed occurrences (all) | 3 / 76 (3.95%) 3 | | |
| Dry Mouth subjects affected / exposed occurrences (all) | 7 / 76 (9.21%) 9 | | |
| Rectal Haemorrhage subjects affected / exposed occurrences (all) | 0 / 76 (0.00%) 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 occurrences (all) | 17 / 76 (22.37%) 20 | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 7 / 76 (9.21%) 7 | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 5 / 76 (6.58%) 8 | | |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 0 / 76 (0.00%) 0 | | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 76 (0.00%) 0 | | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 76 (0.00%) 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 22 May 2013 | <ol style="list-style-type: none">1. The Phase of the study from Phase II to Phase III2. Added that primary endpoint PFS is IRC-Assessed3. Added PFS (Investigator-Assessed) as a secondary endpoint4. Added a pharmacokinetic (PK) sub-study for subjects receiving topotecan in Part 2 of the study5. 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 modified7. An efficacy interim analysis for OS was introduced for Part 2 of the study8. Independent Review Committee was implemented |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported