



Clinical trial results:

A Multi-centre, Open-label, Randomised, Two-arm Phase III Trial of Bevacizumab Plus Chemotherapy Versus Chemotherapy Alone in Patients With Platinum-resistant, Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer.

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2009-011400-33 |
| Trial protocol | SE ES PT DE IT FR DK NL BE FI GR |
| Global end of trial date | 09 July 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 28 April 2022 |
| First version publication date | 28 April 2022 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | MO22224 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00976911 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 July 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 July 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Main objective of the study was to evaluate the efficacy and safety of bevacizumab added to chemotherapy versus chemotherapy alone in participants with epithelial ovarian, fallopian tube or primary peritoneal cancer with disease progression within 6 months of platinum therapy.

Protection of trial subjects:

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

Background therapy:

Both arms in the study received chemotherapy treatment, which was either paclitaxel, topotecan or pegylated liposomal doxorubicin. These treatments were considered to be the standard-of-care non-investigational combination drugs in the study. Liposomal doxorubicin was administered at 40 mg/m² intravenously (iv) every 4 weeks. Paclitaxel was administered at 80 mg/m² iv on days 1, 8, 15 and 22 of each 4-week cycle. Topotecan was administered at 4 mg/m² iv on days 1, 8 and 15 of each 4-week cycle, or 1.25 mg/kg on days 1-5 of each 3-week cycle.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 29 October 2009 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 4 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------------------|
| Country: Number of subjects enrolled | France: 121 |
| Country: Number of subjects enrolled | Germany: 67 |
| Country: Number of subjects enrolled | Spain: 56 |
| Country: Number of subjects enrolled | Denmark: 19 |
| Country: Number of subjects enrolled | Italy: 16 |
| Country: Number of subjects enrolled | Belgium: 14 |
| Country: Number of subjects enrolled | Norway: 14 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 11 |
| Country: Number of subjects enrolled | Sweden: 10 |
| Country: Number of subjects enrolled | Netherlands: 9 |
| Country: Number of subjects enrolled | Portugal: 9 |
| Country: Number of subjects enrolled | Turkey: 9 |
| Country: Number of subjects enrolled | Greece: 5 |
| Country: Number of subjects enrolled | Finland: 1 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 361 |
| EEA total number of subjects | 341 |

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) | 228 |
| From 65 to 84 years | 133 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited at a total of 96 sites in 14 countries in Europe.

Pre-assignment

Screening details:

The study enrolled adult subjects with epithelial ovarian cancer (EOC), fallopian tube carcinoma (FTC) or primary peritoneal carcinomas (PPC) who were considered to have platinum-resistant disease (progression <6 months from last platinum-based therapy).

Period 1

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

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Chemotherapy |

Arm description:

Participants received one of the following chemotherapies at the discretion of the investigator: paclitaxel, 80 milligrams per square meter (mg/m²) as a 1-hour intravenous (IV) infusion on Days 1, 8, 15, and 22 every 4 weeks (q4w) OR topotecan 4 mg/m² as a 30-minute IV infusion on Days 1, 8, and 15 q4w (alternatively, a 1.25 mg/m² dose could have been administered over 30 minutes on Days 1-5 every 3 weeks [q3w]) OR pegylated liposomal doxorubicin (PLD) 40 mg/m² as a 1 milligram per minute (mg/min) infusion on Day 1 q4w (after Cycle 1 the drug could have been administered as a 1 hour infusion). Depending on chosen chemotherapy, pre-medication was implemented according to local practices.

| | |
|---|----------------------------|
| Arm type | Chemotherapy only |
| No investigational medicinal product assigned in this arm | |
| Arm title | Chemotherapy + Bevacizumab |

Arm description:

Participants received one of the following chemotherapies at the discretion of the investigator: paclitaxel, 80 mg/m² as a 1-hour IV infusion on Days 1, 8, 15, and 22 q4w OR topotecan 4 mg/m² as a 30-minute IV infusion on Days 1, 8, and 15 q4w (alternatively, a 1.25 mg/m² dose could have been administered over 30 minutes on Days 1-5 q3w) OR PLD 40 mg/m² as a 1 mg/min infusion on Day 1 q4w (after Cycle 1 the drug could have been administered as a 1 hour infusion). Depending on chosen chemotherapy, pre-medication was implemented according to local practices. The chosen chemotherapy was combined with bevacizumab 10 milligrams per kilogram (mg/kg) IV every 2 weeks (q2w; or bevacizumab 15 mg/kg q3w if used in combination with topotecan 1.25 mg/m² on Days 1-5 on a q3w schedule). The initial bevacizumab infusion was over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes, as tolerated.

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

Dosage and administration details:

Bevacizumab was administered at 10 mg/kg iv every 2 weeks or 15 mg/kg iv every 3 weeks.

| Number of subjects in period 1 | Chemotherapy | Chemotherapy + Bevacizumab |
|---------------------------------------|--------------|-------------------------------|
| Started | 182 | 179 |
| Completed | 0 | 0 |
| Not completed | 182 | 179 |
| Adverse event, serious fatal | 138 | 126 |
| Consent withdrawn by subject | 4 | 6 |
| In Follow-Up as of 25 Jan 2013 | 30 | 37 |
| Adverse event, non-fatal | - | 1 |
| Not Specified | 8 | 9 |
| Protocol deviation | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Chemotherapy |
|-----------------------|--------------|

Reporting group description:

Participants received one of the following chemotherapies at the discretion of the investigator: paclitaxel, 80 milligrams per square meter (mg/m^2) as a 1-hour intravenous (IV) infusion on Days 1, 8, 15, and 22 every 4 weeks (q4w) OR topotecan 4 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 q4w (alternatively, a 1.25 mg/m^2 dose could have been administered over 30 minutes on Days 1-5 every 3 weeks [q3w]) OR pegylated liposomal doxorubicin (PLD) 40 mg/m^2 as a 1 milligram per minute (mg/min) infusion on Day 1 q4w (after Cycle 1 the drug could have been administered as a 1 hour infusion). Depending on chosen chemotherapy, pre-medication was implemented according to local practices.

| | |
|-----------------------|----------------------------|
| Reporting group title | Chemotherapy + Bevacizumab |
|-----------------------|----------------------------|

Reporting group description:

Participants received one of the following chemotherapies at the discretion of the investigator: paclitaxel, 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 q4w OR topotecan 4 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 q4w (alternatively, a 1.25 mg/m^2 dose could have been administered over 30 minutes on Days 1-5 q3w) OR PLD 40 mg/m^2 as a 1 mg/min infusion on Day 1 q4w (after Cycle 1 the drug could have been administered as a 1 hour infusion). Depending on chosen chemotherapy, pre-medication was implemented according to local practices. The chosen chemotherapy was combined with bevacizumab 10 milligrams per kilogram (mg/kg) IV every 2 weeks (q2w; or bevacizumab 15 mg/kg q3w if used in combination with topotecan 1.25 mg/m^2 on Days 1-5 on a q3w schedule). The initial bevacizumab infusion was over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes, as tolerated.

| Reporting group values | Chemotherapy | Chemotherapy + Bevacizumab | Total |
|------------------------------------|--------------|----------------------------|-------|
| Number of subjects | 182 | 179 | 361 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-------------------|--------------------|-----|
| Age Continuous Units: years arithmetic mean standard deviation | 60.7 ± 9.8 | 60.0 ± 11.1 | - |
| Sex: Female, Male Units: Subjects | | | |
| Female | 182 | 179 | 361 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Chemotherapy |
|-----------------------|--------------|

Reporting group description:

Participants received one of the following chemotherapies at the discretion of the investigator: paclitaxel, 80 milligrams per square meter (mg/m^2) as a 1-hour intravenous (IV) infusion on Days 1, 8, 15, and 22 every 4 weeks (q4w) OR topotecan 4 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 q4w (alternatively, a 1.25 mg/m^2 dose could have been administered over 30 minutes on Days 1-5 every 3 weeks [q3w]) OR pegylated liposomal doxorubicin (PLD) 40 mg/m^2 as a 1 milligram per minute (mg/min) infusion on Day 1 q4w (after Cycle 1 the drug could have been administered as a 1 hour infusion). Depending on chosen chemotherapy, pre-medication was implemented according to local practices.

| | |
|-----------------------|----------------------------|
| Reporting group title | Chemotherapy + Bevacizumab |
|-----------------------|----------------------------|

Reporting group description:

Participants received one of the following chemotherapies at the discretion of the investigator: paclitaxel, 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 q4w OR topotecan 4 mg/m^2 as a 30-minute IV infusion on Days 1, 8, and 15 q4w (alternatively, a 1.25 mg/m^2 dose could have been administered over 30 minutes on Days 1-5 q3w) OR PLD 40 mg/m^2 as a 1 mg/min infusion on Day 1 q4w (after Cycle 1 the drug could have been administered as a 1 hour infusion). Depending on chosen chemotherapy, pre-medication was implemented according to local practices. The chosen chemotherapy was combined with bevacizumab 10 milligrams per kilogram (mg/kg) IV every 2 weeks (q2w; or bevacizumab 15 mg/kg q3w if used in combination with topotecan 1.25 mg/m^2 on Days 1-5 on a q3w schedule). The initial bevacizumab infusion was over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes, as tolerated.

Primary: Percentage of Participants with Disease Progression or Death (Data cutoff 14 November 2011)

| | |
|-----------------|--|
| End point title | Percentage of Participants with Disease Progression or Death (Data cutoff 14 November 2011) ^[1] |
|-----------------|--|

End point description:

Progression free survival was defined as the time from the date of randomization to the first documented disease progression or death, whichever occurs first. Progression was based on tumour assessment made by the investigators according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria (for participants with measurable disease), and for those with non-measurable disease presence or absence of lesions was noted. ITT Population: All participants randomized to study treatment, irrespective of whether or not the assigned treatment was actually received.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Screening Visit, Every 8 weeks (or 9 weeks if receiving topotecan) until progression reported between day of first participant randomized (29 October 2009) until cutoff date of 14 November 2011

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: No statistical analysis was planned for this endpoint.

| End point values | Chemotherapy | Chemotherapy + Bevacizumab | | |
|-----------------------------------|-----------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 182 | 179 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 92.3 | 78.2 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (PFS; Data Cutoff 14 November 2011)

| | |
|-----------------|---|
| End point title | Progression Free Survival (PFS; Data Cutoff 14 November 2011) |
|-----------------|---|

End point description:

PFS was defined as the time from the date of randomization to the first documented disease progression (PD) or death, whichever occurred first. Progression was based on tumor assessment made by the investigators according to the RECIST criteria (for participants with measurable disease), and for those with non-measurable disease presence or absence of lesions was noted. An event was defined as the earliest progressive disease or death that occurred on or before the cutoff date (14Nov2011), regardless of start of non-protocol specified anti-cancer therapy or bevacizumab monotherapy. PD was assessed by investigator according to RECIST or by symptom deterioration, and could not be declared based on rising cancer antigen 125 (CA125) levels alone. ITT Population: All randomized participants. Only participants with an event of progression or death were included in the analysis. Kaplan-Meier methodology was used. 95% CI for median was computed using the method of Brookmeyer and Crowley.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Screening Visit, Every 8 weeks (or 9 weeks if receiving topotecan) until progression reported between day of first participant randomized (29 October 2009) until cutoff date of 14 November 2011

| End point values | Chemotherapy | Chemotherapy + Bevacizumab | | |
|----------------------------------|--------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 168 | 141 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.4 (2.10 to 3.75) | 6.8 (5.62 to 7.79) | | |

Statistical analyses

| | |
|----------------------------|---------------------|
| Statistical analysis title | Stratified analysis |
|----------------------------|---------------------|

Statistical analysis description:

Cox regression model was used to determine the hazard ratio.

| | |
|---|---|
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 309 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.379 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.296 |
| upper limit | 0.485 |

Notes:

[2] - Stratified analysis: Strata were: chemotherapy selected (paclitaxel, PLD, or topotecan), prior anti-angiogenic therapy (yes or no), and platinum-free interval (less than [$<$] 3 or 3-6 months).

| | |
|---|---|
| Statistical analysis title | Unstratified analysis |
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 309 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.366 |
| upper limit | 0.577 |

| | |
|---|--|
| Statistical analysis title | Unstratified analysis p-value Peto-Peto-Prentice |
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 309 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Peto-Peto-Prentice |

| | |
|---|--|
| Statistical analysis title | Stratified analysis p-value Peto-Peto-Prentice |
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 309 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Peto-Peto-Prentice |

Secondary: Percentage of Participants with Best Overall Confirmed Objective Response of Complete Response (CR) or Partial Response (PR) per Modified RECIST (Data Cutoff 14 November 2011)

| | |
|-----------------|---|
| End point title | Percentage of Participants with Best Overall Confirmed Objective Response of Complete Response (CR) or Partial Response (PR) per Modified RECIST (Data Cutoff 14 November 2011) |
|-----------------|---|

End point description:

Objective Response was determined by the investigator using modified RECIST criteria, Version 1.0. An objective response was a complete or partial overall confirmed response as determined by investigators.

CR defined as complete disappearance of all target and non-target lesions and no new lesions. PR defined as greater than or equal to (\geq) 30 percent (%) decrease in the sum of appropriate diameters of all target measurable lesions, no progress in the non-measurable disease, and no new lesions. ITT Population; only participants with measurable disease at baseline were included in the analysis. 95% CI computed using the normal approximation to the binomial distribution.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening Visit, Every 8 weeks (or 9 weeks if receiving topotecan) until progression reported between day of first participant randomized (29 October 2009) until cutoff date of 14 November 2011

| End point values | Chemotherapy | Chemotherapy + Bevacizumab | | |
|-----------------------------------|--------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 144 | 142 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 12.5 (7.1 to 17.9) | 28.2 (20.8 to 35.6) | | |

Statistical analyses

| Statistical analysis title | Difference in Response Rates |
|---|---|
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 15.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.5 |
| upper limit | 24.8 |

| Statistical analysis title | Unstratified Analysis p-value |
|---|---|
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 ^[3] |
| Method | Pearson's chi-square |

Notes:

[3] - Unstratified

| Statistical analysis title | Stratified Analysis p-value |
|----------------------------|---|
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 286 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0007 ^[4] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[4] - Stratified analysis: Strata were: chemotherapy selected (paclitaxel, PLD, or topotecan), prior anti-angiogenic therapy (yes or no), and platinum-free interval (<3 or 3-6 months).

Secondary: Duration of Objective Response (Data Cutoff 14 November 2011)

| | |
|-----------------|---|
| End point title | Duration of Objective Response (Data Cutoff 14 November 2011) |
|-----------------|---|

End point description:

For randomized participants who achieved an objective response per modified RECIST, duration of objective response was defined as the time from the date of the first occurrence of a CR or PR (whichever occurred first) until the date that progressive disease or death was documented (whichever occurred first). Participants who had an objective response and did not experience disease progression or death by the time of analysis were censored at the time of the last tumor assessment. ITT Population; only participants with a best overall confirmed response of CR or PR were included in the analysis. Summaries of duration of objective response (median and percentiles) were estimated from Kaplan–Meier curves. 95% CI for duration of objective response was computed using the method of Brookmeyer and Crowley.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening Visit, Every 8 weeks (or 9 weeks if receiving topotecan) until progression reported between day of first participant randomized (29 October 2009) until cutoff date of 14 November 2011

| End point values | Chemotherapy | Chemotherapy + Bevacizumab | | |
|----------------------------------|--------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 40 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.4 (3.81 to 9.23) | 9.4 (6.60 to 11.63) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Unstratified Peto-Peto-Prentice p-value |
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0081 |
| Method | Peto-Peto-Prentice |

| | |
|-----------------------------------|--|
| Statistical analysis title | Unstratified Hazard Ratio - Log Rank p-value |
|-----------------------------------|--|

Statistical analysis description:

Cox regression model was used to determine the hazard ratio.

| | |
|---|---|
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0202 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.225 |
| upper limit | 0.9 |

Secondary: Percentage of Participants Who Died (Data Cutoff 25 January 2013)

| | |
|--|---|
| End point title | Percentage of Participants Who Died (Data Cutoff 25 January 2013) |
| End point description: | |
| ITT Population: All participants randomized to study treatment, irrespective of whether or not the assigned treatment was actually received. | |
| End point type | Secondary |
| End point timeframe: | |
| Screening Visit, Every 8 weeks (or 9 weeks if receiving topotecan) until progression reported between day of first participant randomized (29 October 2009) until cutoff date of 25 January 2013 | |

| End point values | Chemotherapy | Chemotherapy + Bevacizumab | | |
|-----------------------------------|-----------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 182 | 179 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 75.8 | 71.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (Data Cutoff 25 January 2013)

| | |
|--|--|
| End point title | Overall Survival (Data Cutoff 25 January 2013) |
| End point description: | |
| Duration of overall survival was defined as the time from randomization to death of any cause. Kaplan-Meier methodology was used. The OS data for participants for whom no death was captured in the clinical database were censored at the last time they were known to be alive. ITT Population; only participants who died were included in the analysis. 95% CI was computed using the method of Brookmeyer and Crowley. | |
| End point type | Secondary |

End point timeframe:

Screening Visit, Every 8 weeks (or 9 weeks if receiving topotecan) until progression reported between day of first participant randomized (29 October 2009) until cutoff date of 25 January 2013

| End point values | Chemotherapy | Chemotherapy + Bevacizumab | | |
|----------------------------------|-----------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 138 | 128 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 13.3 (11.89 to 16.43) | 16.6 (13.70 to 18.99) | | |

Statistical analyses

| Statistical analysis title | Unstratified Hazard Ratio - Log Rank p-value |
|---|--|
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.136 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.833 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.655 |
| upper limit | 1.059 |

| Statistical analysis title | Unstratified Peto-Peto-Prentice p-value |
|---|---|
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0715 |
| Method | Peto-Peto-Prentice |

| Statistical analysis title | Stratified Hazard Ratio - Log Rank p-value |
|--|--|
| Statistical analysis description: | |
| Stratified analysis: Strata were: chemotherapy selected (paclitaxel, PLD, or topotecan), prior anti-angiogenic therapy (yes or no), and platinum-free interval (<3 or 3-6 months). | |
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |

| | |
|---|-------------------|
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2711 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.678 |
| upper limit | 1.116 |

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | Stratified Peto-Peto-Prentice p-value |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Stratified analysis: Strata were: chemotherapy selected (paclitaxel, PLD, or topotecan), prior anti-angiogenic therapy (yes or no), and platinum-free interval (<3 or 3-6 months).

| | |
|---|---|
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.089 |
| Method | Peto-Peto-Prentice |

Secondary: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Ovarian (OV) 28 Abdominal/Gastrointestinal (AB/GI) Symptom Scale - Percentage of Responders (Data Cutoff 14 November 2011)

| | |
|-----------------|---|
| End point title | European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Ovarian (OV) 28 Abdominal/Gastrointestinal (AB/GI) Symptom Scale - Percentage of Responders (Data Cutoff 14 November 2011) |
|-----------------|---|

End point description:

The EORTC OV-28 module is a questionnaire that focuses on issues specific to ovarian cancer. Participants were asked to indicate the extent to which they experienced AB/GI symptoms in the week prior to assessment. Participants responded on a scale of 1-4 (1=not at all, 2=a little, 3=quite a bit, 4=very much) to the following: Did you have abdominal pain? Did you have a bloated feeling in your abdomen/stomach? Did you have problems with your clothes feeling too tight? Did you experience any change in bowel habit due to your disease or treatment? Were you troubled by passing wind/gas/flatulence? Have you felt full too quickly after beginning to eat? Have you had indigestion/heartburn? Data are transformed to a scale from 0 to 100. Lower scores represent fewer symptoms. Participants were considered a responder if they had a 10 point or more reduction in score from baseline. ITT population; n indicates the number of participants who completed the questionnaire at the specified visit.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Weeks 8, 9, 16, 18, 24 and 30 (Data Cutoff 14 November 2011)

| End point values | Chemotherapy | Chemotherapy + Bevacizumab | | |
|-----------------------------------|---------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 84 | 122 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Weeks 8/9 (n=84,122) | 19.0 (11.3 to 29.1) | 27.9 (20.1 to 36.7) | | |
| Weeks 16/18 (n=43,86) | 23.3 (11.8 to 38.6) | 26.7 (17.8 to 37.4) | | |
| Week 24 (n=22,53) | 22.7 (7.8 to 45.4) | 32.1 (19.9 to 46.3) | | |
| Week 30 (n=12,42) | 33.3 (9.9 to 65.1) | 28.6 (15.7 to 44.6) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Responders at Baseline versus Week 8/9 |
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1859 |
| Method | Fisher exact |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 8.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.8 |
| upper limit | 21.4 |

| | |
|---|---|
| Statistical analysis title | Responders at Baseline versus Week 16/18 |
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.8309 |
| Method | Fisher exact |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 3.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14 |
| upper limit | 20.9 |

| | |
|---|---|
| Statistical analysis title | Responders at Baseline versus Week 24 |
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.579 |
| Method | Fisher exact |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 9.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15 |
| upper limit | 34.1 |

| | |
|---|---|
| Statistical analysis title | Responders at Baseline versus Week 30 |
| Comparison groups | Chemotherapy v Chemotherapy + Bevacizumab |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7339 |
| Method | Fisher exact |
| Parameter estimate | Difference in Response Rates |
| Point estimate | -4.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -40 |
| upper limit | 30.6 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded at every treatment visit and all follow-up visits until 2 months after the final follow-up visit (up to approximately 4 years).

Adverse event reporting additional description:

AEs: Safety population: all treated up to 25Jan2013 CCOD. Additional AEs: 26Jan2013 to 09Jul1014 in the primary study period: no SAEs; 8 Grade 2-3 AEs (blurred vision, fatigue, bronchitis, gastroenteritis, dehydration, proteinuria, hypertension, hyponatremia) in 4 subjects in the CT+BV arm. Deaths (all causes): ITT population up to 09Jul2014 CCOD.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Chemotherapy |
|-----------------------|--------------|

Reporting group description:

Participants received one of the following chemotherapies at the discretion of the investigator: paclitaxel, 80 mg/m² as a 1-hour IV infusion on Days 1, 8, 15, and 22 q4w OR topotecan 4 mg/m² as a 30-minute IV infusion on Days 1, 8, and 15 q4w (alternatively, a 1.25 mg/m² dose could have been administered over 30 minutes on Days 1-5 q3w) OR PLD 40 mg/m² as a 1 mg/min infusion on Day 1 q4w (after Cycle 1 the drug could have been administered as a 1 hour infusion). Depending on chosen chemotherapy, pre-medication was implemented according to local practices.

| | |
|-----------------------|----------------------------|
| Reporting group title | Chemotherapy + Bevacizumab |
|-----------------------|----------------------------|

Reporting group description:

Participants received one of the following chemotherapies at the discretion of the investigator: paclitaxel, 80 mg/m² as a 1-hour IV infusion on Days 1, 8, 15, and 22 q4w OR topotecan 4 mg/m² as a 30-minute IV infusion on Days 1, 8, and 15 q4w (alternatively, a 1.25 mg/m² dose could have been administered over 30 minutes on Days 1-5 q3w) OR PLD 40 mg/m² as a 1 mg/min infusion on Day 1 q4w (after Cycle 1 the drug could have been administered as a 1 hour infusion). Depending on chosen chemotherapy, pre-medication was implemented according to local practices. The chosen chemotherapy was combined with bevacizumab 10 mg/kg IV q2w (or bevacizumab 15 mg/kg q3w if used in combination with topotecan 1.25 mg/m² on Days 1-5 on a q3w schedule). The initial bevacizumab infusion was over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes, as tolerated.

| Serious adverse events | Chemotherapy | Chemotherapy + Bevacizumab | |
|---|-------------------|----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 49 / 181 (27.07%) | 56 / 179 (31.28%) | |
| number of deaths (all causes) | 152 | 144 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Hypertension | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 4 / 179 (2.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism arterial | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism venous | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |

| | | | |
|--|-----------------|-----------------|--|
| Cytoreductive surgery | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 3 / 179 (1.68%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 3 / 179 (1.68%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site necrosis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General symptom | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Immune system disorders | | | |
| Food allergy | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Female genital tract fistula | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 2 / 179 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 4 / 179 (2.23%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 2 / 179 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 179 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 2 / 179 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 5 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Wrong drug administered | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Arrhythmia supraventricular subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac arrest subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Coronary artery disease subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders Depressed level of consciousness subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 181 (2.76%) | 4 / 179 (2.23%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 4 / 179 (2.23%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 6 / 181 (3.31%) | 4 / 179 (2.23%) | |
| occurrences causally related to treatment / all | 1 / 6 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 3 / 179 (1.68%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 2 / 179 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 181 (3.87%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal hypomotility | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic ascites | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileal perforation | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileal stenosis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Vesical fistula | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 2 / 179 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Musculoskeletal and connective tissue disorders | | | |
| Bone disorder | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 179 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious peritonitis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 179 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 179 (1.12%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 179 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Chemotherapy | Chemotherapy + Bevacizumab | |
|---|--------------------|----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 129 / 181 (71.27%) | 146 / 179 (81.56%) | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 11 / 179 (6.15%) | |
| occurrences (all) | 5 | 11 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 10 / 181 (5.52%) | 32 / 179 (17.88%) | |
| occurrences (all) | 10 | 43 | |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 13 / 181 (7.18%) | 32 / 179 (17.88%) | |
| occurrences (all) | 17 | 35 | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 25 / 181 (13.81%) | 23 / 179 (12.85%) | |
| occurrences (all) | 41 | 49 | |
| Anaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 46 / 181 (25.41%) | 35 / 179 (19.55%) | |
| occurrences (all) | 74 | 54 | |
| Neutropenia | | | |
| subjects affected / exposed | 44 / 181 (24.31%) | 55 / 179 (30.73%) | |
| occurrences (all) | 78 | 171 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 12 / 181 (6.63%) | 10 / 179 (5.59%) | |
| occurrences (all) | 23 | 20 | |
| General disorders and administration site conditions | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| Fatigue subjects affected / exposed occurrences (all) | 46 / 181 (25.41%) 57 | 49 / 179 (27.37%) 66 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 10 / 181 (5.52%) 16 | 23 / 179 (12.85%) 25 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 15 / 181 (8.29%) 16 | 17 / 179 (9.50%) 23 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 4 / 181 (2.21%) 4 | 9 / 179 (5.03%) 10 | |
| Constipation subjects affected / exposed occurrences (all) | 17 / 181 (9.39%) 21 | 13 / 179 (7.26%) 14 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 10 / 181 (5.52%) 17 | 17 / 179 (9.50%) 26 | |
| Vomiting subjects affected / exposed occurrences (all) | 15 / 181 (8.29%) 21 | 14 / 179 (7.82%) 17 | |
| Nausea subjects affected / exposed occurrences (all) | 13 / 181 (7.18%) 17 | 17 / 179 (9.50%) 19 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 9 / 181 (4.97%) 9 | 10 / 179 (5.59%) 12 | |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 181 (0.00%) 0 | 9 / 179 (5.03%) 9 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 11 / 181 (6.08%) 11 | 15 / 179 (8.38%) 15 | |

| | | | |
|---|--|---|--|
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 9 / 181 (4.97%) 10 | 19 / 179 (10.61%) 20 | |
| Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) | 1 / 181 (0.55%) 1 | 22 / 179 (12.29%) 42 | |
| Infections and infestations Infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 6 / 181 (3.31%) 8 13 / 181 (7.18%) 17 | 19 / 179 (10.61%) 22 15 / 179 (8.38%) 20 | |
| Metabolism and nutrition disorders Decreased appetite alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 14 / 181 (7.73%) 19 | 10 / 179 (5.59%) 12 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 November 2009 | The definition of platinum resistance was made more specific: progression within < 6 months from completion of a minimum of 4 platinum therapy cycles, with the date calculated from the last administered dose of platinum therapy. The definition of prior therapies was clarified to include all previous anti-cancer therapy, including those received in the front-line or recurrent settings. It was clarified that it was not a requirement in RECIST for the same investigator to evaluate the participant at each assessment. The statistical analysis for the primary endpoint was updated from a one- to a two-sided log-rank test. The numbers of participants randomized to chemotherapy cohorts was amended because of statistical changes to include 120 participants per chemotherapy cohort. The timing of QoL assessments was amended to be more suited to the scheduling of cycle visits, the 3 worst symptom questionnaire was collected at baseline only, and the use of the 3 worst symptom questionnaire methodology was described in more detail. The protocol was updated so that all Grade 2 adverse events were collected. It was clarified how a participant who had been previously enrolled in a blinded study with an anti-angiogenic was to be stratified. The frequency of CA-125 assessments was corrected to be performed every cycle, not at every visit. It was clarified that the "optional post-study phase" for participants randomized to the CT arm was for the CT arm only and that bevacizumab was to be given as part of the study to those participants who opted to receive crossover bevacizumab monotherapy. Additional safety guidance was provided for the management of bevacizumab in the event of CNS bleeding, proteinuria management, and hypersensitivity with paclitaxel. The definition of residual disease was amended based on the presence or absence of macroscopic disease. Definitions of progression for participants with measurable and non-measurable disease at randomization were further detailed. |
| 28 October 2010 | Clarification regarding the exclusion criteria for platinum refractory disease, peripheral neuropathy, and previous malignancies. Addition of left ventricular ejection fraction (LVEF) assessments every fourth cycle for participants receiving pegylated liposomal doxorubicin (PLD). Additional requirement to capture certain concomitant medication in the electronic Case Report Form (eCRF), particularly supportive medication prescribed for the treatment of cancer-related symptoms or potential side effects of chemotherapy. Clarification that only serious adverse events caused by protocol-mandated interventions needed to be collected prior to initiation of study medication and that all serious adverse events needed to be collected before, during, and after study drug dosing. Guidance on dose modification to reflect the bevacizumab safety profile. Clarification to ensure that only those participants who experienced disease progression on chemotherapy alone were able to subsequently receive bevacizumab on the bevacizumab crossover option. |
| 23 January 2013 | Allow for a potential retrospective scan collection and a review of scans by an independent review committee (IRC). Clarify that the duration of survival follow-up should continue for a minimum of 12 months after end of treatment for all participants. |
| 05 December 2013 | The amendment defined that the study would be closed as soon as the protocol amendment was approved by regulatory authorities and Ethics Committees. The amendment clarified that participants who were still receiving investigational study medication (bevacizumab) would end their AURELIA study participation. If the Avastin Long Term Extension study (AvaLTE, MO25757) was approved in the participant's country, the participant would be offered participation in this study. Alternatively the participant would be offered continued bevacizumab treatment with commercial drug until disease progression, unacceptable toxicity or participant request for discontinuation as initially planned by the protocol. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported