



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
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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
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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
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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
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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
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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]
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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
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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)
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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
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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
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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)
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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
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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)
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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
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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
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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
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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)
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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
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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 09Jul2014 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Chemotherapy
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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
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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			
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	
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	
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	
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	
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	
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 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	
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	
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			
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	
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	
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	
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	
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			
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	
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	
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			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	46 / 181 (25.41%)	35 / 179 (19.55%)	
occurrences (all)	74	54	
Leukopenia			
subjects affected / exposed	25 / 181 (13.81%)	23 / 179 (12.85%)	
occurrences (all)	41	49	
Thrombocytopenia			
subjects affected / exposed	12 / 181 (6.63%)	10 / 179 (5.59%)	
occurrences (all)	23	20	
Neutropenia			
subjects affected / exposed	44 / 181 (24.31%)	55 / 179 (30.73%)	
occurrences (all)	78	171	
General disorders and administration site conditions			

Mucosal inflammation subjects affected / exposed occurrences (all)	10 / 181 (5.52%) 16	23 / 179 (12.85%) 25	
Fatigue subjects affected / exposed occurrences (all)	46 / 181 (25.41%) 57	49 / 179 (27.37%) 66	
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 181 (2.21%) 4	9 / 179 (5.03%) 10	
Abdominal pain subjects affected / exposed occurrences (all)	15 / 181 (8.29%) 16	17 / 179 (9.50%) 23	
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	
Nausea subjects affected / exposed occurrences (all)	13 / 181 (7.18%) 17	17 / 179 (9.50%) 19	
Vomiting subjects affected / exposed occurrences (all)	15 / 181 (8.29%) 21	14 / 179 (7.82%) 17	
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