Clinical trial results:
A Single-Arm Phase II Clinical Study Of The Combination Of Carboplatin And Weekly Paclitaxel Plus Bevacizumab As First-Line Treatment In Patients With Epithelial Ovarian Cancer

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2008-008336-85
Trial protocol	FR NL GB SE IT
Global end of trial date	29 July 2013

Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	07 August 2015
Version creation reason	• Correction of full data set QC of the full data set to address the errors identified after the system was unavailable

Trial information

Trial identification

Sponsor protocol code	MO22225

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00937560
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	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, 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	29 July 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this single arm study was to evaluate the efficacy and safety of first-line chemotherapy with carboplatin and dose-dense weekly paclitaxel plus bevacizumab (Avastin) in participants with epithelial ovarian, fallopian tube, or primary peritoneal cancer. The primary outcome measure was progression-free survival (PFS). Secondary outcome measures were objective response (OR), duration of response (DR), overall survival (OS) at 1 and 2 years, biological progression-free interval (BPFI), and adverse events and safety assessments.

Protection of trial subjects:

This study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the participant. This study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" (GCP) International Conference on Harmonization (ICH) Tripartite Guideline (January 1997), or with local law if it afforded greater protection to the participant. For studies conducted in the European/ European Economic Area (EU/EEA) countries, investigators ensured compliance with the European (EU) Clinical Trial Directive (2001/20/EC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Sweden: 22
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	189
EEA total number of subjects	132

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)	152
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Potential participants were screened from 55 centers in Brazil, France, Italy, The Netherlands, Norway, Russia, Spain, Sweden, and the United Kingdom. One of the 190 enrolled participants withdrew consent before receiving treatment and was therefore not included in the analyzed Intent-to-treat (ITT) population of 189 participants.

Period 1

Period 1 title	Initial Treatment Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Bevacizumab + Paclitaxel + Carboplatin

Arm description:

Participants received bevacizumab 7.5 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3-week cycle for a maximum of 17 cycles. Participants also received paclitaxel (80 milligrams per square meter [mg/m^2] IV) on Days 1, 8, and 15 and carboplatin IV (area under the curve of 6) on Day 1 of each 3-week cycle for a maximum of 8 cycles. The initial dose of carboplatin was calculated according to the Calvert formula (mg = [glomerular filtration rate + 25] x 6).

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:

Participants received bevacizumab 7.5 mg/kg IV on Day 1 of each 3-week cycle for a maximum of 17 cycles.

Number of subjects in period 1	Bevacizumab + Paclitaxel + Carboplatin
Started	189
Completed	168
Not completed	21
No end of study page	10
Death	6
Adverse event	1
Withdrawn consent	3
Lost to follow-up	1

Period 2

Period 2 title	Maintenance Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Bevacizumab + Paclitaxel + Carboplatin

Arm description:

Participants received bevacizumab 7.5 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3-week cycle for a maximum of 17 cycles. Participants also received paclitaxel (80 milligrams per square meter [mg/m^2] IV) on Days 1, 8, and 15 and carboplatin IV (area under the curve of 6) on Day 1 of each 3-week cycle for a maximum of 8 cycles. The initial dose of carboplatin was calculated according to the Calvert formula (mg = [glomerular filtration rate + 25] x 6).

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:

Participants received bevacizumab 7.5 mg/kg IV on Day 1 of each 3-week cycle for a maximum of 17 cycles.

Number of subjects in period 2	Bevacizumab + Paclitaxel + Carboplatin
Started	168
Completed	150
Not completed	18
Consent withdrawn by subject	5
According to protocol	1
Death	12

Baseline characteristics

Reporting groups	
Reporting group title	Initial Treatment Phase

Reporting group description: -

Reporting group values	Initial Treatment Phase	Total	
Number of subjects	189	189	
Age categorical Units: Subjects			
Age continuous			
Baseline age of the ITT population			
Units: years median full range (min-max)	 55 24 to 79	 -	
Gender categorical			
Baseline gender of ITT population			
Units: Subjects			
Female	189	189	
Male	0	0	

End points

End points reporting groups

Reporting group title	Bevacizumab + Paclitaxel + Carboplatin

Reporting group description:

Participants received bevacizumab 7.5 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3-week cycle for a maximum of 17 cycles. Participants also received paclitaxel (80 milligrams per square meter [mg/m^2] IV) on Days 1, 8, and 15 and carboplatin IV (area under the curve of 6) on Day 1 of each 3-week cycle for a maximum of 8 cycles. The initial dose of carboplatin was calculated according to the Calvert formula (mg = [glomerular filtration rate + 25] x 6).

Reporting group title	Bevacizumab + Paclitaxel + Carboplatin

Reporting group description:

Participants received bevacizumab 7.5 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3-week cycle for a maximum of 17 cycles. Participants also received paclitaxel (80 milligrams per square meter [mg/m^2] IV) on Days 1, 8, and 15 and carboplatin IV (area under the curve of 6) on Day 1 of each 3-week cycle for a maximum of 8 cycles. The initial dose of carboplatin was calculated according to the Calvert formula (mg = [glomerular filtration rate + 25] x 6).

Primary: Progression-free Survival

End point title	Progression-free Survival[1]

End point description:

Progression-free survival was defined as the time from the first administration of any study treatment to the first disease progression using Response Evaluation Criteria in Solid Tumors (RECIST) or death from any cause, whichever occurred first. This analysis included the ITT population defined as all enrolled participants who received at least one dose of any study medication (carboplatin or paclitaxel or bevacizumab).

End point type	Primary

End point timeframe:

Baseline to the data cut-off date of 19 Jul 2012 for analysis of the primary Outcome Measure (follow-up time up to 3 years, 1 month)

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: This was a single arm treatment group study, therefore, a statistical analysis of the primary end point was not completed.

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	189			
Units: Months				
median (confidence interval 90%)	23.7 (19.9 to 26.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an Objective Response

End point title	Percentage of Participants With an Objective Response

End point description:

An objective response was defined as either a complete response (CR) or a partial response (PR). Using RECIST, a CR was defined as the disappearance of all target lesions and all non-target lesions, normalization of tumor marker level, and no new lesions and a PR was defined as the disappearance of all target lesions and persistence of greater than or equal to (≥)1 non-target lesions and/or the maintenance of tumor marker level above the normal limits, or, at least a 30 percent (%) decrease in the sum of the longest diameter of target lesions, and no new lesions or unequivocal progression of existing non-target lesions. Only participants with measurable disease were included in the analysis according to RECIST only. Only participants with a baseline ovarian cancer mucin CA-125 level ≥2 times the upper limit of normal (ULN) who had a ≥50% reduction of CA-125 from baseline were included in the analysis according to CA-125 level.

End point type	Secondary

End point timeframe:

Baseline, CA-125: every treatment visit before study drug administration, 30 days after last dose, and every 3 months; RECIST: at end of 3rd and 6th cycles, at Months 9 and 12, and every 6 months until end of study (up to a maximum of 36 months)

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	126[2]			
Units: Percentage of Participants				
number (confidence interval 95%)				
RECIST response (n=91)	84.6 (75.5 to 91.3)			
CA-125 and/or RECIST response (n=126)	92.1 (85.9 to 96.1)			
CA-125 only response (n=101)	97 (91.6 to 99.4)			

Notes:

[2] - ITT Population; n=number of participants analyzed for the referenced parameter.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was defined as the interval between the date of the first documented response by RECIST to the date of first disease progression or death, whichever occurred earlier. Disease progression was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or the appearance of 1 or more new lesions, or the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Only participants with measurable disease were included in the analysis according to RECIST only. Only participants with a baseline ovarian cancer mucin CA-125 level ≥ 2 times the ULN who had a ≥ 50% reduction of CA-125 from baseline were included in the analysis according to CA-125 level.

End point type	Secondary

End point timeframe:

Baseline, CA-125: every treatment visit before study drug administration, 30 days after last dose, and every 3 months; RECIST: at end of 3rd and 6th cycles, at Months 9 and 12, and every 6 months until end of study (up to a maximum of 36 months)

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	116[3]			
Units: Months				
median (confidence interval 95%)				
RECIST responders (n=77)	14.7 (12.7 to 16.1)			
CA-125 and/or RECIST responders (n=116)	17.4 (15.4 to 21.9)			
CA-125 only responders (n=98)	17.5 (15.4 to 21.9)			

Notes:

[3] - ITT Population; n=number of participants analyzed for the referenced parameter.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 1 Year and 2 Years

End point title	Overall Survival at 1 Year and 2 Years
End point description:	
Time to death by any cause.	
End point type	Secondary
End point timeframe:	
Year 1 and Year 2	

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	189[4]			
Units: Percentage of Participants				
number (confidence interval 95%)				
Year 1	97.8 (95.7 to 99.9)			
Year 2	92.3 (88.4 to 96.2)			

Notes:

[4] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Biological Progression-free Interval (BPFI)

End point title	Biological Progression-free Interval (BPFI)

End point description:

BPFI defined as the interval from the date of the first administration of any study treatment to the date of the first documented serial elevation of the ovarian cancer mucin CA-125. Precisely it is the first documented increase in CA-125 levels as follows: (1) CA-125 ≥2 times the ULN on 2 occasions at least 1 week apart (CA-125 within normal range pre-treatment) or (2) CA-125 ≥2 times the ULN on 2 occasions at least 1 week apart (elevated CA-125 pre-treatment and initial normalization of CA-125 on-treatment) or (3) CA-125 ≥2 times the nadir value, which is the lowest observed CA-125 value per participant on 2 occasions at least 1 week apart (elevated CA-125 pre-treatment which never normalized). 9999=median and 95% confidence interval was not reached as greater than 80% of participants were censored.

End point type	Secondary

End point timeframe:

Baseline, every treatment visit before study drug administration, 30 days after last dose, and every 3 months (up to a maximum of 36 months)

End point values	Bevacizumab + Paclitaxel + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	189[5]			
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)			

Notes:

[5] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to the end of the study (up to 49 months)	
Adverse event reporting additional description:	
Safety population: All enrolled participants who received at least 1 dose of any study medication (bevacizumab, carboplatin, or paclitaxel).	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Bevacizumab + Paclitaxel + Carboplatin
Reporting group description:	
Participants received bevacizumab 7.5 mg/kg IV on Day 1 of each 3-week cycle for a maximum of 17 cycles. Participants also received paclitaxel (80 mg/m^2 IV) on Days 1, 8, and 15 and carboplatin IV (area under the curve of 6) on Day 1 of each 3-week cycle for a maximum of 8 cycles. The initial dose of carboplatin was calculated according to the Calvert formula (mg = [glomerular filtration rate + 25] x 6).	

Serious adverse events	Bevacizumab + Paclitaxel + Carboplatin		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 189 (22.75%)		
number of deaths (all causes)	32		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Second primary malignancy			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism venous			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 189 (1.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Chest discomfort			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	2 / 189 (1.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 189 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 189 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 189 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Postoperative adhesion				
subjects affected / exposed	1 / 189 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 189 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 189 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral infarction				
subjects affected / exposed	1 / 189 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Cerebral ischaemia			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial aneurysm			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 189 (2.65%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	2 / 189 (1.06%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Subileus			
subjects affected / exposed	3 / 189 (1.59%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			
subjects affected / exposed	2 / 189 (1.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal perforation			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 189 (1.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Cellulitis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected lymphocele			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bevacizumab + Paclitaxel + Carboplatin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	186 / 189 (98.41%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	44 / 189 (23.28%)		
occurrences (all)	61		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	105 / 189 (55.56%)		
occurrences (all)	170		

Asthenia subjects affected / exposed occurrences (all)	22 / 189 (11.64%) 38		
Pyrexia subjects affected / exposed occurrences (all)	19 / 189 (10.05%) 20		
Mucosal inflammation subjects affected / exposed occurrences (all)	15 / 189 (7.94%) 19		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	76 / 189 (40.21%) 105		
Dysphonia subjects affected / exposed occurrences (all)	10 / 189 (5.29%) 14		
Cough subjects affected / exposed occurrences (all)	13 / 189 (6.88%) 13		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	12 / 189 (6.35%) 13		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	19 / 189 (10.05%) 33		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	14 / 189 (7.41%) 25		
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	80 / 189 (42.33%) 94		
Headache			

subjects affected / exposed	34 / 189 (17.99%)		
occurrences (all)	42		
Paraesthesia			
subjects affected / exposed	25 / 189 (13.23%)		
occurrences (all)	33		
Dysgeusia			
subjects affected / exposed	22 / 189 (11.64%)		
occurrences (all)	25		
Dizziness			
subjects affected / exposed	14 / 189 (7.41%)		
occurrences (all)	16		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	153 / 189 (80.95%)		
occurrences (all)	471		
Thrombocytopenia			
subjects affected / exposed	85 / 189 (44.97%)		
occurrences (all)	211		
Anaemia			
subjects affected / exposed	111 / 189 (58.73%)		
occurrences (all)	191		
Leukopenia			
subjects affected / exposed	48 / 189 (25.40%)		
occurrences (all)	121		
Lymphopenia			
subjects affected / exposed	14 / 189 (7.41%)		
occurrences (all)	32		
Thrombocytosis			
subjects affected / exposed	11 / 189 (5.82%)		
occurrences (all)	23		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	87 / 189 (46.03%)		
occurrences (all)	183		
Diarrhoea			

subjects affected / exposed	59 / 189 (31.22%)		
occurrences (all)	129		
Constipation			
subjects affected / exposed	64 / 189 (33.86%)		
occurrences (all)	98		
Stomatitis			
subjects affected / exposed	39 / 189 (20.63%)		
occurrences (all)	73		
Vomiting			
subjects affected / exposed	43 / 189 (22.75%)		
occurrences (all)	72		
Abdominal pain			
subjects affected / exposed	31 / 189 (16.40%)		
occurrences (all)	60		
Abdominal pain upper			
subjects affected / exposed	20 / 189 (10.58%)		
occurrences (all)	22		
Gingival bleeding			
subjects affected / exposed	13 / 189 (6.88%)		
occurrences (all)	14		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	89 / 189 (47.09%)		
occurrences (all)	91		
Rash			
subjects affected / exposed	16 / 189 (8.47%)		
occurrences (all)	44		
Nail disorder			
subjects affected / exposed	15 / 189 (7.94%)		
occurrences (all)	15		
Erythema			
subjects affected / exposed	10 / 189 (5.29%)		
occurrences (all)	11		
Nail toxicity			
subjects affected / exposed	11 / 189 (5.82%)		
occurrences (all)	11		

Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 11 / 189 (5.82%) 18		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all)	 42 / 189 (22.22%) 57 28 / 189 (14.81%) 36 18 / 189 (9.52%) 20 18 / 189 (9.52%) 19 11 / 189 (5.82%) 12 10 / 189 (5.29%) 11		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 21 / 189 (11.11%) 28 18 / 189 (9.52%) 21 17 / 189 (8.99%) 19		
Metabolism and nutrition disorders Hyperglycaemia			

subjects affected / exposed	16 / 189 (8.47%)		
occurrences (all)	37		
Decreased appetite			
subjects affected / exposed	19 / 189 (10.05%)		
occurrences (all)	32		
Hypokalaemia			
subjects affected / exposed	16 / 189 (8.47%)		
occurrences (all)	31		
Hypercholesterolaemia			
subjects affected / exposed	12 / 189 (6.35%)		
occurrences (all)	21		
Hypoalbuminaemia			
subjects affected / exposed	11 / 189 (5.82%)		
occurrences (all)	18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2009	The first amendment (Protocol Version 2) had the following key elements: - Clarified the definition for date of debulking surgery and staging in participants who had undergone two abdominal operations - Clarified the presence of symptomatic central nervous system metastases as an exclusion criterion - Added that a serious active infection requiring intravenous antibiotics at enrollment as an exclusion criterion
24 November 2009	The second amendment (Protocol Version 3) included the following key elements: - Clarified the treatment duration: Total maximum bevacizumab duration limited to 17 cycles - Clarified the timing and method of baseline tumor evaluation and collection and grading of adverse events and laboratory parameters - Clarified that after progression, the only concomitant therapies to be recorded were anti-cancer therapies - Added guidelines for monitoring serum creatinine, definition of the ITT population, and transfer of the database after final database lock

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported