Clinical trial results:
A Multicenter Open-Label Single-Arm Phase II Study Evaluating the Safety and Efficacy of Bevacizumab in Combination With Carboplatin and Paclitaxel in Patients With Metastatic, Recurrent or Persistent Cervical Cancer

Summary

EudraCT number	2014-005491-28
Trial protocol	ES PT PL GR FR BG IT
Global end of trial date	31 December 2018

Results information

Result version number	v1 (current)
This version publication date	27 December 2019
First version publication date	27 December 2019

Trial information

Trial identification

Sponsor protocol code	MO29594

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02467907
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	31 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2018
Global end of trial reached?	Yes
Global end of trial date	31 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to determine the safety of bevacizumab in combination with carboplatin and paclitaxel therapy for metastatic, recurrent or persistent cervical cancer, as defined by the frequency and severity of gastrointestinal (GI) perforation/fistula, GI-vaginal fistula and genitourinary (GU) fistula events.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 July 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	Costa Rica: 4
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Panama: 7
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Turkey: 7

Worldwide total number of subjects	150
EEA total number of subjects	79

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)	131
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

222 patients were screened for this study and 150 received study treatment.

Period 1

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

Arms

Arm title	Bevacizumab in Combination with Carboplatin and Paclitaxel

Arm description:

Administration of bevacizumab, carboplatin and paclitaxel once every 3 weeks, for at least 6 cycles, until disease progression (as assessed by the investigator), unacceptable toxicity, physician or participant decision or withdrawal of consent. If either chemotherapy or bevacizumab is discontinued, the participant may continue to receive the other ongoing therapy.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin, RO4876646
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous (i.v.) administration of 15 mg/kg bevacizumab once every 3 weeks

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administration of carboplatin at 5 milligrams per milliliter*minute (mg/mL*min) on Day 1 every 3 weeks for at least 6 cycles

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administration of paclitaxel at a dose of 175 milligrams per square meter (mg/m^2) on Day 1 every 3 weeks for at least 6 cycles

Number of subjects in period 1	Bevacizumab in Combination with Carboplatin and Paclitaxel
Started	150
Completed	41
Not completed	109
Physician decision	4
Consent withdrawn by subject	23
Death	71
Sponsor decision	1
Lost to follow-up	10

Baseline characteristics

Reporting groups	
Reporting group title	Bevacizumab in Combination with Carboplatin and Paclitaxel
Reporting group description:	
Administration of bevacizumab, carboplatin and paclitaxel once every 3 weeks, for at least 6 cycles, until disease progression (as assessed by the investigator), unacceptable toxicity, physician or participant decision or withdrawal of consent. If either chemotherapy or bevacizumab is discontinued, the participant may continue to receive the other ongoing therapy.	

Reporting group values	Bevacizumab in Combination with Carboplatin and Paclitaxel	Total	
Number of subjects	150	150	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	131	131	
From 65-84 years	19	19	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	50.4		
standard deviation	± 11.60	-	
Gender categorical Units: Subjects			
Female	150	150	
Male	0	0	

End points

End points reporting groups

Reporting group title	Bevacizumab in Combination with Carboplatin and Paclitaxel

Reporting group description:

Administration of bevacizumab, carboplatin and paclitaxel once every 3 weeks, for at least 6 cycles, until disease progression (as assessed by the investigator), unacceptable toxicity, physician or participant decision or withdrawal of consent. If either chemotherapy or bevacizumab is discontinued, the participant may continue to receive the other ongoing therapy.

Primary: Percentage of Participants with GI Perforation/Fistula, GI-Vaginal Fistula and GU Fistula Events

End point title	Percentage of Participants with GI Perforation/Fistula, GI-Vaginal Fistula and GU Fistula Events[1]

End point description:

End point type	Primary

End point timeframe:

Baseline up to 24 months

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: There was no formal statistical test / hypothesis testing specified.

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (confidence interval 95%)				
All perforation/fistula	11.3 (6.7 to 17.5)			
GI perforation/fistula	4.7 (1.9 to 9.4)			
GI-vaginal fistula	4.0 (1.5 to 8.5)			
GU fistula	4.7 (1.9 to 9.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with GI Perforation/Fistula, GI-Vaginal Fistula and GU Fistula Events According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0

End point title	Percentage of Participants with GI Perforation/Fistula, GI-Vaginal Fistula and GU Fistula Events According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0[2]

End point description:

End point type	Primary

End point timeframe:

Baseline up to 24 months

Notes:

[2] - 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: There was no formal statistical test / hypothesis testing specified.

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
GI perforation/fistula (All Grades)	4.7			
GI perforation/fistula (Grade 3)	1.3			
GI perforation/fistula (Grade 4)	1.3			
GI perforation/fistula (Grade 5)	0.7			
GI-vaginal fistula (All Grades)	4.0			
GI-vaginal fistula (Grade 3)	2.0			
GI-vaginal fistula (Grade 4)	0			
GI-vaginal fistula (Grade 5)	0			
GU fistula (All Grades)	4.7			
GU fistula (Grade 3)	2.0			
GU fistula (Grade 4)	0			
GU fistula (Grade 5)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Time to First GI Perforation/Fistula, GI-Vaginal Fistula or GU Fistula Events

End point title	Time to First GI Perforation/Fistula, GI-Vaginal Fistula or GU Fistula Events[3]

End point description:

End point type	Primary

End point timeframe:

Baseline up to 24 months

Notes:

[3] - 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: There was no formal statistical test / hypothesis testing specified.

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: months				
arithmetic mean (standard deviation)				
First perforation/fistula (N=17)	4.24 (± 3.118)			
First GI perforation/fistula (N=7)	4.23 (± 2.694)			
First GI-vaginal fistula (N=6)	3.75 (± 2.049)			
First GU fistula (N=7)	5.05 (± 4.083)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Intensity (Ratio of Actual Dose Administered Versus Intended Dose) for Bevacizumab During the Treatment Period

End point title	Dose Intensity (Ratio of Actual Dose Administered Versus Intended Dose) for Bevacizumab During the Treatment Period

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of intended dose				
arithmetic mean (standard deviation)	100.014 (± 0.1568)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Intensity (Ratio of Actual Dose Administered Versus Intended Dose) for Carboplatin During the Treatment Period

End point title	Dose Intensity (Ratio of Actual Dose Administered Versus Intended Dose) for Carboplatin During the Treatment Period

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of intended dose				
arithmetic mean (standard deviation)	98.290 (± 4.3623)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Intensity (Ratio of Actual Dose Administered Versus Intended Dose) for Paclitaxel During the Treatment Period

End point title	Dose Intensity (Ratio of Actual Dose Administered Versus Intended Dose) for Paclitaxel During the Treatment Period

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of intended dose				
arithmetic mean (standard deviation)	98.274 (± 5.3525)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Treatment for Bevacizumab

End point title	Duration of Treatment for Bevacizumab

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: months				
arithmetic mean (standard deviation)	9.58 (± 8.874)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Treatment for Carboplatin

End point title	Duration of Treatment for Carboplatin

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: months				
arithmetic mean (standard deviation)	4.26 (± 2.286)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Treatment for Paclitaxel

End point title	Duration of Treatment for Paclitaxel

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: months				
arithmetic mean (standard deviation)	4.27 (± 2.386)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AEs)

End point title	Percentage of Participants with Adverse Events (AEs)

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (confidence interval 95%)	98.0 (94.3 to 99.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Serious Adverse Events (SAEs)

End point title	Percentage of Participants with Serious Adverse Events (SAEs)

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (confidence interval 95%)	31.3 (24.0 to 39.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events of Special Interest (AESIs)

End point title	Percentage of Participants with Adverse Events of Special Interest (AESIs)

End point description:

AESIs included arterial thromboembolic events (ATE), bleeding, heart failure (CHF)/left ventricular systolic dysfunction, febrile neutropenia, hypertension, proteinuria, posterior reversible encephalopathy syndrome (PRES), venous thromboembolic event; and wound-healing complication.

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (confidence interval 95%)	82.7 (75.6 to 88.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with AEs Leading to Treatment Interruption or Permanent discontinuation

End point title	Percentage of Participants with AEs Leading to Treatment Interruption or Permanent discontinuation

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: percentage of participants				
number (not applicable)				
Discontinuation of Bevacizumab	32.0			
Discontinuation of Paclitaxel/Platin	28.0			
Interruption of Bevacizumab	42.7			
Interruption of Paclitaxel/Platin	46.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Count of Participants that Died during Study

End point title	Count of Participants that Died during Study

End point description:

End point type	Secondary
End point timeframe: Baseline up to 24 months	

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: participants				
number (not applicable)				
Disease Progression Adverse Event	61 8			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) According to Response Evaluation Criteria for Solid Tumors (RECIST) Version 1.1

End point title	Progression-Free Survival (PFS) According to Response Evaluation Criteria for Solid Tumors (RECIST) Version 1.1
End point description: PFS is defined as time from the first dose of study treatment [bevacizumab or chemotherapy] to the first occurrence of investigator-assessed disease progression (PD) according to RECIST v1.1 or death from any cause.	
End point type	Secondary
End point timeframe: Baseline up to 24 months	

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: months				
median (confidence interval 95%)	10.9 (10.1 to 13.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival is defined as the time from first study drug (bevacizumab or chemotherapy) to death due to any cause

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: months				
median (confidence interval 95%)	25.0 (20.9 to 30.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Best Overall Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.1

End point title	Percentage of Participants with a Best Overall Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.1

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Bevacizumab in Combination with Carboplatin and Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	138			
Units: percentage of participants				
number (confidence interval 95%)				

Complete Response Partial Response	13.8 (8.5 to 20.7) 47.1 (38.6 to 55.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 24 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Bevacizumab in Combination with Carboplatin and Paclitaxel

Reporting group description:

Administration of bevacizumab, carboplatin and paclitaxel once every 3 weeks, for at least 6 cycles, until disease progression (as assessed by the investigator), unacceptable toxicity, physician or participant decision or withdrawal of consent. If either chemotherapy or bevacizumab is discontinued, the participant may continue to receive the other ongoing therapy.

Serious adverse events	Bevacizumab in Combination with Carboplatin and Paclitaxel		
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 150 (31.33%)		
number of deaths (all causes)	74		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
RADIATION PROCTITIS			
subjects affected / exposed	1 / 150 (0.67%)		
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 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
HYPERTENSION			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
HYPOTENSION			

subjects affected / exposed	2 / 150 (1.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
HYPOVOLAEMIC SHOCK				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
CEREBROVASCULAR ACCIDENT				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
DEPRESSED LEVEL OF CONSCIOUSNESS				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Blood and lymphatic system disorders				
ANAEMIA				
subjects affected / exposed	6 / 150 (4.00%)			
occurrences causally related to treatment / all	5 / 6			
deaths causally related to treatment / all	0 / 0			
FEBRILE NEUTROPENIA				
subjects affected / exposed	3 / 150 (2.00%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	1 / 1			
LEUKOPENIA				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
NEUTROPENIA				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

PANCYTOPENIA			
subjects affected / exposed	2 / 150 (1.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
THROMBOCYTOPENIA			
subjects affected / exposed	3 / 150 (2.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
SUPRAPUBIC PAIN			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ANAL FISTULA			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
AORTOENTERIC FISTULA			

subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
COLITIS			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
CONSTIPATION			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GASTROINTESTINAL PERFORATION			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
LOWER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
NAUSEA			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
RECTAL HAEMORRHAGE			

subjects affected / exposed	4 / 150 (2.67%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
VOMITING			
subjects affected / exposed	2 / 150 (1.33%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
FEMALE GENITAL TRACT FISTULA			
subjects affected / exposed	4 / 150 (2.67%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
METRORRHAGIA			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
PELVIC PAIN			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
UTERINE HAEMORRHAGE			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
VAGINAL HAEMORRHAGE			
subjects affected / exposed	3 / 150 (2.00%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
VULVOVAGINAL PAIN			
subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

PNEUMOTHORAX				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
PULMONARY EMBOLISM				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
ACUTE KIDNEY INJURY				
subjects affected / exposed	2 / 150 (1.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
ANURIA				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
HAEMATURIA				
subjects affected / exposed	2 / 150 (1.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
HYDRONEPHROSIS				
subjects affected / exposed	2 / 150 (1.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT OBSTRUCTION				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
UROGENITAL FISTULA				
subjects affected / exposed	5 / 150 (3.33%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue				

disorders				
BACK PAIN				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
ABSCESS SOFT TISSUE				
subjects affected / exposed	2 / 150 (1.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
PERITONITIS				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SOFT TISSUE INFECTION				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT INFECTION				
subjects affected / exposed	4 / 150 (2.67%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
UROSEPSIS				
subjects affected / exposed	1 / 150 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
DEHYDRATION				

subjects affected / exposed	1 / 150 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPOKALAEMIA			
subjects affected / exposed	1 / 150 (0.67%)		
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 in Combination with Carboplatin and Paclitaxel		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 150 (96.67%)		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	52 / 150 (34.67%)		
occurrences (all)	91		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	38 / 150 (25.33%)		
occurrences (all)	64		
FATIGUE			
subjects affected / exposed	26 / 150 (17.33%)		
occurrences (all)	31		
MUCOSAL INFLAMMATION			
subjects affected / exposed	10 / 150 (6.67%)		
occurrences (all)	14		
OEDEMA PERIPHERAL			
subjects affected / exposed	11 / 150 (7.33%)		
occurrences (all)	13		
PYREXIA			
subjects affected / exposed	10 / 150 (6.67%)		
occurrences (all)	12		
Immune system disorders			

DRUG HYPERSENSITIVITY			
subjects affected / exposed	8 / 150 (5.33%)		
occurrences (all)	13		
Reproductive system and breast disorders			
PELVIC PAIN			
subjects affected / exposed	12 / 150 (8.00%)		
occurrences (all)	18		
Respiratory, thoracic and mediastinal disorders			
EPISTAXIS			
subjects affected / exposed	31 / 150 (20.67%)		
occurrences (all)	38		
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	8 / 150 (5.33%)		
occurrences (all)	8		
INSOMNIA			
subjects affected / exposed	8 / 150 (5.33%)		
occurrences (all)	12		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	8 / 150 (5.33%)		
occurrences (all)	11		
BLOOD CREATININE INCREASED			
subjects affected / exposed	12 / 150 (8.00%)		
occurrences (all)	19		
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	19 / 150 (12.67%)		
occurrences (all)	32		
PLATELET COUNT DECREASED			
subjects affected / exposed	17 / 150 (11.33%)		
occurrences (all)	22		
WEIGHT DECREASED			
subjects affected / exposed	12 / 150 (8.00%)		
occurrences (all)	12		
WHITE BLOOD CELL COUNT DECREASED			

subjects affected / exposed	10 / 150 (6.67%)		
occurrences (all)	19		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	29 / 150 (19.33%)		
occurrences (all)	45		
NEUROPATHY PERIPHERAL			
subjects affected / exposed	37 / 150 (24.67%)		
occurrences (all)	43		
PARAESTHESIA			
subjects affected / exposed	20 / 150 (13.33%)		
occurrences (all)	24		
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	18 / 150 (12.00%)		
occurrences (all)	36		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	70 / 150 (46.67%)		
occurrences (all)	104		
LEUKOPENIA			
subjects affected / exposed	27 / 150 (18.00%)		
occurrences (all)	45		
NEUTROPENIA			
subjects affected / exposed	53 / 150 (35.33%)		
occurrences (all)	103		
THROMBOCYTOPENIA			
subjects affected / exposed	41 / 150 (27.33%)		
occurrences (all)	68		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	25 / 150 (16.67%)		
occurrences (all)	41		
CONSTIPATION			
subjects affected / exposed	41 / 150 (27.33%)		
occurrences (all)	54		
DIARRHOEA			

subjects affected / exposed occurrences (all) GINGIVAL BLEEDING subjects affected / exposed occurrences (all) HAEMORRHOIDS subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) RECTAL HAEMORRHAGE subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all)	45 / 150 (30.00%) 73 12 / 150 (8.00%) 15 8 / 150 (5.33%) 9 66 / 150 (44.00%) 136 8 / 150 (5.33%) 11 51 / 150 (34.00%) 85		
Skin and subcutaneous tissue disorders ALOPECIA subjects affected / exposed occurrences (all) RASH subjects affected / exposed occurrences (all)	 70 / 150 (46.67%) 73 11 / 150 (7.33%) 17		
Renal and urinary disorders HAEMATURIA subjects affected / exposed occurrences (all) PROTEINURIA subjects affected / exposed occurrences (all)	 12 / 150 (8.00%) 15 29 / 150 (19.33%) 51		
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) BACK PAIN	 42 / 150 (28.00%) 77 		

subjects affected / exposed	16 / 150 (10.67%)		
occurrences (all)	23		
BONE PAIN			
subjects affected / exposed	13 / 150 (8.67%)		
occurrences (all)	21		
MYALGIA			
subjects affected / exposed	32 / 150 (21.33%)		
occurrences (all)	47		
PAIN IN EXTREMITY			
subjects affected / exposed	11 / 150 (7.33%)		
occurrences (all)	13		
Infections and infestations			
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	11 / 150 (7.33%)		
occurrences (all)	12		
URINARY TRACT INFECTION			
subjects affected / exposed	22 / 150 (14.67%)		
occurrences (all)	30		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	21 / 150 (14.00%)		
occurrences (all)	37		
HYPERURICAEMIA			
subjects affected / exposed	10 / 150 (6.67%)		
occurrences (all)	12		
HYPOMAGNESAEMIA			
subjects affected / exposed	21 / 150 (14.00%)		
occurrences (all)	33		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2016	Protocol was amended with inclusion of an independent radiology review of MRI scans and other minor changes.
12 July 2018	Protocol was amended to clarify eligibility criteria, update information on continued access to bevacizumab and update the medical monitor for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported