



Clinical trial results:

An Open-Label, Single-Arm, Phase II Study to Evaluate the Efficacy and the Feasibility of Bevacizumab (Avastin®) Based on a FOLFOXIRI Regimen Until Progression in Patients with Previously Untreated Metastatic Colorectal Carcinoma (OPAL-Study)

Summary

EudraCT number	2008-001180-11
Trial protocol	DE
Global end of trial date	20 February 2014

Results information

Result version number	v1 (current)
This version publication date	31 May 2020
First version publication date	31 May 2020

Trial information

Trial identification

Sponsor protocol code	ML20514
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00940303
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	20 February 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 February 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluation of progression-free survival (PFS) of bevacizumab combined with treatment regimen consisting of 5-fluorouracil (5-FU)/folinic acid (FA), oxaliplatin and irinotecan (FOLFOXIRI) regimen in subjects with previously untreated metastatic colorectal carcinoma.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy:

Treatment with 5-FU/FA, oxaliplatin and irinotecan (FOLFOXIRI) administered by intravenous (IV) infusion for 12 cycles once every 2 weeks, followed by up to 40 cycles once every 2 weeks of 5-FU/FA IV infusion.

Evidence for comparator: -

Actual start date of recruitment	06 July 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	63

From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited at study sites in Germany.

Pre-assignment

Screening details:

Participants with histologically confirmed diagnosis of metastatic colorectal carcinoma (CRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria were eligible for the study.

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
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Arm description:

Participants received IV infusion of bevacizumab on Day 1 of each cycle prior to the infusion of background medication for up to 52 cycles once every 2 weeks.

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:

5 milligram per kilogram (mg/kg) body weight administered as IV infusion on Day 1 of each cycle prior to the infusion of background medication for up to 52 cycles once every 2 weeks.

Number of subjects in period 1	Bevacizumab
Started	90
Completed	27
Not completed	63
Consent withdrawn by subject	1
Death	44
Lost to follow-up	18

Baseline characteristics

Reporting groups

Reporting group title	Bevacizumab
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Reporting group description:

Participants received IV infusion of bevacizumab on Day 1 of each cycle prior to the infusion of background medication for up to 52 cycles once every 2 weeks.

Reporting group values	Bevacizumab	Total	
Number of subjects	90	90	
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	57.9 ± 8.9	-	
Gender Categorical Units: Subjects			
Female	26	26	
Male	64	64	

End points

End points reporting groups

Reporting group title	Bevacizumab
Reporting group description:	
Participants received IV infusion of bevacizumab on Day 1 of each cycle prior to the infusion of background medication for up to 52 cycles once every 2 weeks.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS) ^[1]
End point description:	
PFS is defined as the time from the start of treatment to disease progression (PD), relapse or death from any cause, whichever occurs first, as per the Response Evaluation Criteria in Solid Tumors (RECIST). PD was defined as a 20 percent or greater increase in the sum of the longest diameter of the target lesions taking as reference the smallest sum longest diameter recorded or appearance of new lesions. Intent-to-treat (ITT) population included all participants who had received at least one dose of the study medication.	
End point type	Primary
End point timeframe:	
From start of treatment up to disease progression or relapse or death, whichever occurred first (up to approximately 55 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: Only descriptive statistics were planned for this endpoint.	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: months				
median (confidence interval 95%)	11.1 (9.4 to 12.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS is defined as the time from the start of study treatment to death from any cause. ITT population included all participants who had received at least one dose of the study medication.	
End point type	Secondary
End point timeframe:	
From start of treatment up to death of any cause (approximately 55 months)	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: months				
median (confidence interval 95%)	32.2 (22.6 to 37.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Among Resected Participants Who Had R0 Resection

End point title	Percentage of Participants Among Resected Participants Who Had R0 Resection
End point description:	
Reported here is the percentage of participants who had curative (R0) resection among those participants who were resected during the study. The population analyzed here included participants who had received at least one dose of the study medication and who had undergone tumor resection during the study.	
End point type	Secondary
End point timeframe:	
Up to approximately 55 months	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: percentage of participants				
number (confidence interval 95%)	66.7 (44.7 to 84.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate
End point description:	
ORR was defined as the percentage of participants with complete response (CR) or partial response (PR) per RECIST criteria. CR was defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must have decreased to normal (short axis <10 millimetres [mm]). No new lesions. PR was defined as at least 30 percent decrease under baseline of the sum of diametres of all target lesions. The short axis was used in the sum for target nodes, while the longest diameter was used in the sum for all other target lesions. ITT population included all participants who had received at least one dose of the study medication.	
End point type	Secondary

End point timeframe:

From start of treatment until disease progression (up to approximately 55 months)

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: percentage of participants				
number (confidence interval 95%)	64.4 (53.7 to 74.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate

End point title	Best Overall Response Rate
End point description:	
Best overall response was defined as the percentage of participants with CR + PR + stable disease (SD) per RECIST criteria. CR was defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must have decreased to normal (short axis <10 millimetres [mm]). No new lesions. PR was defined as at least 30 percent decrease under baseline of the sum of diameters of all target lesions. The short axis was used in the sum for target nodes, while the longest diameter was used in the sum for all other target lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. ITT population included all participants who had received at least one dose of the study medication.	
End point type	Secondary
End point timeframe:	
Treatment start until disease progression/recurrence (up to approximately 55 months)	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: percentage of participants				
number (confidence interval 95%)	86.7 (77.9 to 92.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response

End point title	Duration of Overall Response
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End point description:

Duration of overall response was defined as the time from first documented objective response (CR or PR), whichever status was recorded first until the first date on which recurrence or PD was objectively documented. CR was defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must have decreased to normal (short axis <10 millimetres [mm]). No new lesions. PR was defined as at least 30 percent decrease under baseline of the sum of diametres of all target lesions. The short axis was used in the sum for target nodes, while the longest diameter was used in the sum for all other target lesions. ITT Population included all participants who had received at least one dose of the study medication.

End point type	Secondary
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End point timeframe:

Treatment start until disease progression/recurrence (approximately 55 months)

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	58 ^[2]			
Units: days				
median (confidence interval 95%)	274 (244 to 313)			

Notes:

[2] - Number of participants analysed are the participants who were evaluated for the endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Change in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Percentage of Participants with Change in Eastern Cooperative Oncology Group (ECOG) Performance Status
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End point description:

ECOG performance status was assessed by investigator as 0: fully active, able to carry out all pre-disease performance without restriction, 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework office work, 2: restricted physical activity, capable of all self-care, but unable to carry out any work activities. Up and about >50 of waking hours, 3: capable of only limited self-care; confined to bed or chair >50% of waking hours. 4: completely disabled; cannot carry out any self-care; totally confined to bed or chair. ITT population included all participants who had received at least one dose of the study medication.

End point type	Secondary
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End point timeframe:

Screening, Safety Follow up (up to Week 107)

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	84 ^[3]			
Units: percentage of participants				
number (not applicable)				
Worsened	33.3			
Unchanged	58.3			

Improved	8.3			
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Notes:

[3] - Number of participants analysed are the participants who were evaluated for the endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treatment Cycles with Study Medication

End point title	Number of Treatment Cycles with Study Medication
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End point description:

End point type	Secondary
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End point timeframe:

Up to end of treatment period (up to Week 103)

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: treatment cycles				
arithmetic mean (standard deviation)				
Bevacizumab	15.1 (± 11.8)			
Oxaliplatin	9.1 (± 3.5)			
Irinotecan	9.2 (± 3.5)			
Folinic acid	14.9 (± 11.3)			
5-FU	14.9 (± 11.3)			

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)
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End point description:

An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. Safety population included all participants who received at least one dose of the study medication and had at least one safety follow-up, regardless whether the trial medication was prematurely withdrawn or not.

End point type	Secondary
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End point timeframe:

Up to approximately 55 months

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: percentage of participants				
number (not applicable)	98.9			

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)
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End point description:

AESIs were defined as diarrhoea of grade 2 according to the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) v3.0 as well as any grade of gastrointestinal perforation, gastrointestinal fistulas or other internal fistulas, wound-healing disturbances, haemorrhagic events and arterial thromboembolic events. Safety population included all participants who received at least one dose of the study medication and had at least one safety follow-up, regardless whether the trial medication was prematurely withdrawn or not.

End point type	Secondary
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End point timeframe:

Up to approximately 55 months

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: percentage of participants				
number (not applicable)	51.1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 55 months

Adverse event reporting additional description:

Safety population was defined as the participants who received at least one dose of the study medication and had at least one safety follow-up, regardless whether the trial medication was prematurely withdrawn or not.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	Bevacizumab
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Reporting group description:

Participants received IV infusion of bevacizumab on Day 1 of each cycle prior to the infusion of background medication for up to 52 cycles once every 2 weeks.

Serious adverse events	Bevacizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 90 (43.33%)		
number of deaths (all causes)	44		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Stent removal			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hernia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mucosal inflammation			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Impaired healing			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Postoperative wound complication			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemianopia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 90 (3.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Diarrhoea				
subjects affected / exposed	10 / 90 (11.11%)			
occurrences causally related to treatment / all	4 / 11			
deaths causally related to treatment / all	0 / 0			
Diarrhoea haemorrhagic				
subjects affected / exposed	1 / 90 (1.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	1 / 90 (1.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	1 / 90 (1.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	1 / 90 (1.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	4 / 90 (4.44%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	7 / 90 (7.78%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 90 (1.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				

subjects affected / exposed	6 / 90 (6.67%)		
occurrences causally related to treatment / all	2 / 7		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary fistula			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Portal vein thrombosis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			

subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal candidiasis			
subjects affected / exposed	1 / 90 (1.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 90 (2.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pseudomembranous colitis			
subjects affected / exposed	1 / 90 (1.11%)		
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 / 90 (1.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 90 (1.11%)		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 90 (98.89%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 90 (20.00%)		
occurrences (all)	24		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	10		
Fatigue			
subjects affected / exposed	35 / 90 (38.89%)		
occurrences (all)	56		
Mucosal inflammation			
subjects affected / exposed	20 / 90 (22.22%)		
occurrences (all)	30		
Pain			
subjects affected / exposed	7 / 90 (7.78%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	10 / 90 (11.11%)		
occurrences (all)	15		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 90 (10.00%)		
occurrences (all)	11		
Dyspnoea			
subjects affected / exposed	6 / 90 (6.67%)		
occurrences (all)	7		
Epistaxis			
subjects affected / exposed	16 / 90 (17.78%)		
occurrences (all)	19		
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	7 / 90 (7.78%) 7		
Investigations Weight decreased subjects affected / exposed occurrences (all)	11 / 90 (12.22%) 11		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Polyneuropathy subjects affected / exposed occurrences (all)	11 / 90 (12.22%) 30 7 / 90 (7.78%) 9 15 / 90 (16.67%) 51 13 / 90 (14.44%) 79 43 / 90 (47.78%) 69		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	10 / 90 (11.11%) 10 22 / 90 (24.44%) 48 37 / 90 (41.11%) 95 5 / 90 (5.56%) 6		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	5 / 90 (5.56%) 8		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	23 / 90 (25.56%) 32		
Constipation subjects affected / exposed occurrences (all)	15 / 90 (16.67%) 30		
Diarrhoea subjects affected / exposed occurrences (all)	59 / 90 (65.56%) 184		
Dyspepsia subjects affected / exposed occurrences (all)	9 / 90 (10.00%) 10		
Dysphagia subjects affected / exposed occurrences (all)	8 / 90 (8.89%) 11		
Nausea subjects affected / exposed occurrences (all)	58 / 90 (64.44%) 149		
Stomatitis subjects affected / exposed occurrences (all)	16 / 90 (17.78%) 53		
Vomiting subjects affected / exposed occurrences (all)	27 / 90 (30.00%) 76		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	17 / 90 (18.89%) 21		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	5 / 90 (5.56%) 6		

Pain in extremity subjects affected / exposed occurrences (all)	6 / 90 (6.67%) 7		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	18 / 90 (20.00%) 24		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	19 / 90 (21.11%) 27 8 / 90 (8.89%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2008	For clarity the term "bi-weekly" was replaced by the term "once every 2 weeks" in the dosing regimen. During the treatment phase response evaluation, including surgical evaluation, was performed according to RECIST criteria every 8 weeks. Criteria that should lead to discontinuation or early termination of the study were described in more detail.
12 September 2013	The sections of the study protocol about early study termination were amended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 February 2014	The study was terminated prematurely. because the results of the study could not be published before completion of the follow-up of two remaining participants in the study. All other participants had completed their survival follow-up, died, or were lost to follow-up for unknown reason. The last 2 participants had completed their treatment phase and safety follow-up at week 4 following the last administration of bevacizumab. The remaining visits of the survival follow-up of these two participants were cancelled due to study termination.	-

Notes:

Limitations and caveats

None reported