Clinical trial results:
A Phase II, Multicenter, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of RO5520985 (Vanucizumab) Plus FOLFOX Versus Bevacizumab Plus FOLFOX in Patients With Previously Untreated Metastatic Colorectal Cancer

Summary

EudraCT number	2013-005108-32
Trial protocol	BE AT ES IT GB
Global end of trial date	01 February 2017

Results information

Result version number	v1
This version publication date	29 July 2017
First version publication date	29 July 2017

Trial information

Trial identification

Sponsor protocol code	BP29262

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02141295
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche Ltd
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 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	Interim
Date of interim/final analysis	29 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2016
Global end of trial reached?	Yes
Global end of trial date	01 February 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Study BP29262 is to estimate the efficacy of RO5520985 in combination with oxaliplatin, folinic acid, and 5 fluorouracil (mFOLFOX-6) vs. bevacizumab in combination with mFOLFOX-6, as measured by progression-free survival (PFS).

Protection of trial subjects:

This study was fully adhered to the principles outlined in "Guideline for Good Clinical Practice" International Conference on Harmonization (ICH) Tripartite Guideline (January 1997) or with local law.

Background therapy:

mFOLFOX
Both arms received mFOLFOX as background therapy.
In the induction therapy, participants received oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Evidence for comparator:

Bevacizumab

Actual start date of recruitment	30 June 2014
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	Spain: 105
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United States: 59
Country: Number of subjects enrolled	Australia: 5
Worldwide total number of subjects	189
EEA total number of subjects	125

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)	101
From 65 to 84 years	88
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with previously untreated metastatic colorectal cancer (mCRC) as defined by RECIST v1.1 were enrolled globally from 7 countries.

Period 1

Period 1 title	Overall study (part 2) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Vanucizumab + mFOLFOX-6

Arm description:

In the induction therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Arm type	Experimental
Investigational medicinal product name	Vanucizumab
Investigational medicinal product code	
Other name	RO5520985
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2000 mg as IV infusion

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

Dosage and administration details:

85 mg/m^2 as IV infusion

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion

Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m^2 as IV infusion

Arm title	Bevacizumab + mFOLFOX-6

Arm description:

In the induction therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 milligram per kilogram (mg/kg) as IV infusion

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

Dosage and administration details:

85 mg/m^2 as IV infusion

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion

Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m^2 as IV infusion

Number of subjects in period 1	Vanucizumab + mFOLFOX-6	Bevacizumab + mFOLFOX-6
Started	94	95
Completed	17	21
Not completed	77	74
Physician decision	17	12
Consent withdrawn by subject	9	4
Adverse event, non-fatal	16	10
TBC	5	9
Non-compliance	1	-
Study terminated by sponsor	-	1
Progressive disease	29	38

Baseline characteristics

Reporting groups

Reporting group title	Vanucizumab + mFOLFOX-6

Reporting group description:

In the induction therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Reporting group title	Bevacizumab + mFOLFOX-6

Reporting group description:

In the induction therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Reporting group values	Vanucizumab + mFOLFOX-6	Bevacizumab + mFOLFOX-6	Total
Number of subjects	94	95	189
Age Categorical Units: Subjects			
Adults (18-64 years)	48	53	101
From 65-84 years	46	42	88
Age Continuous Units: years			
arithmetic mean	62.7	62.3	
standard deviation	± 11	± 10.6	-
Gender Categorical Units: Subjects			
Female	38	57	95
Male	56	38	94

Subject analysis sets

Subject analysis set title	Safety run-in (part 1)
Subject analysis set type	Safety analysis

Subject analysis set description:

8 eligible participants received 2000 milligrams (mg) vanucizumab + mFOLFOX-6 every two weeks for up to 8 cycles in order to confirm the dose and schedule for the overall study.

Reporting group values	Safety run-in (part 1)		
Number of subjects	8		

Age Categorical Units: Subjects			
Adults (18-64 years)	4		
From 65-84 years	4		
Age Continuous Units: years			
arithmetic mean	63.3		
standard deviation	± 10.8		
Gender Categorical Units: Subjects			
Female	3		
Male	5		

End points

End points reporting groups

Reporting group title	Vanucizumab + mFOLFOX-6

Reporting group description:

In the induction therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Reporting group title	Bevacizumab + mFOLFOX-6

Reporting group description:

In the induction therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Subject analysis set title	Safety run-in (part 1)
Subject analysis set type	Safety analysis

Subject analysis set description:

8 eligible participants received 2000 milligrams (mg) vanucizumab + mFOLFOX-6 every two weeks for up to 8 cycles in order to confirm the dose and schedule for the overall study.

Primary: Progression-free Survival (PFS), time to event

End point title	Progression-free Survival (PFS), time to event

End point description:

Efficacy of vanucizumab was evaluated in terms of PFS as Investigator-Assessed Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).

End point type	Primary

End point timeframe:

Baseline, every 8 weeks, up to approximately 29 months

End point values	Vanucizumab + mFOLFOX-6	Bevacizumab + mFOLFOX-6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	95		
Units: Number of days				
median (confidence interval 95%)	343 (304 to 386)	333 (263 to 388)		

Statistical analyses

Statistical analysis title	Stratified analysis (metastatic sites from IVRS)

Statistical analysis description:

Kaplan-Meier methods were used to estimate median PFS for each treatment arm and the 95% CIs for median PFS were computed using the Brookmeyer and Crowley method.
The stratified Cox proportional hazard was used to estimate the hazard ratio (i.e., the magnitude of the treatment effect) and the corresponding 95% confidence interval. The stratification factors are number of metastatic sites (1 vs. >1) and country/region (USA vs rest of the world).

Comparison groups	Bevacizumab + mFOLFOX-6 v Vanucizumab + mFOLFOX-6
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7581 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.44

Notes:

[1] - log-rank

Secondary: Percentage of Participants With Objective Response (ORR) as Assessed Using RECIST v. 1.1

End point title	Percentage of Participants With Objective Response (ORR) as Assessed Using RECIST v. 1.1

End point description:

Efficacy of vanucizumab was evaluated in terms of Percentage of Participants With ORR as Investigator-Assessed Using RECIST v. 1.1. Best Overall Confirmed Response.

End point type	Secondary

End point timeframe:

Baseline (within 28 days prior to Day 1), then every 8 weeks until progressive disease (PD), start of other anticancer therapy, withdrawal of consent, or death (up to approximately 29 months)

End point values	Vanucizumab + mFOLFOX-6	Bevacizumab + mFOLFOX-6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	95		
Units: Percentage of participants				
number (confidence interval 95%)				
Responders, total	41.5 (31.53 to 51.45)	45.3 (35.25 to 55.27)		
Complete response (CR)	0 (0 to 3.85)	3.2 (0.66 to 8.95)		
Partial response (PR)	41.5 (31.41 to 52.12)	42.1 (32.04 to 52.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response, as Assessed Using RECIST v. 1.1

End point title	Duration of Objective Response, as Assessed Using RECIST v. 1.1

End point description:

Efficacy of vanucizumab was evaluated in terms of duration of objective response as assessed using RECIST v. 1.1.
This was computed using the PFS definition with death on study (deaths that occurred outside the 30 days window from the last study treatment are excluded).

End point type	Secondary

End point timeframe:

Baseline (within 28 days prior to Day 1), then every 8 weeks until PD, start of other anticancer therapy, withdrawal of consent, or death (up to approximately 29 months)

End point values	Vanucizumab + mFOLFOX-6	Bevacizumab + mFOLFOX-6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	95		
Units: days				
median (confidence interval 95%)	282 (274 to 453)	315 (220 to 392)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Efficacy of vanucizumab was evaluated in terms of OS as the time from randomization until death from any cause.
99999 = data not estimable because there were only few deaths in both treatment arms (immature data).

End point type	Secondary

End point timeframe:

Baseline until death from any cause (maximum up to approximately 3.5 years)

End point values	Vanucizumab + mFOLFOX-6	Bevacizumab + mFOLFOX-6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	95		
Units: days				
median (confidence interval 95%)	622 (622 to 99999)	630 (630 to 99999)		

Statistical analyses

Statistical analysis title	Stratified analysis (metastatic sites from IVRS)

Statistical analysis description:

Kaplan-Meier methods were used to estimate median OS for each treatment arm and the 95% CIs for median OS were computed using the Brookmeyer and Crowley method.
The stratified Cox proportional hazard was used to estimate the hazard ratio (i.e., the magnitude of the treatment effect) and the corresponding 95% confidence interval. The stratification factors are number of metastatic sites (1 vs. >1) and country/region (USA vs rest of the world).

Comparison groups	Vanucizumab + mFOLFOX-6 v Bevacizumab + mFOLFOX-6
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5626
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.6

Secondary: Percentage of Participants With Adverse Events (AEs)

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

End point description:

Safety is evaluated in terms of percentage of participants with at least one serious adverse event and percentage of participants with at least one adverse event.

End point type	Secondary

End point timeframe:

Up to approximately 29 months

End point values	Vanucizumab + mFOLFOX-6	Bevacizumab + mFOLFOX-6	Safety run-in (part 1)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	93	95	8	
Units: Percentage of participants				
number (not applicable)				
Serious Adverse events	44.1	42.1	37.5	
Adverse events	100	100	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Human Anti-human Antibodies (HAHAs) Against Vanucizumab

End point title	Number of Participants With Human Anti-human Antibodies (HAHAs) Against Vanucizumab[2]

End point description:

Safety is evaluated in terms of number of participants with Human Anti-human Antibodies (HAHAs) Against Vanucizumab.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours [hrs]) on Day 1 Cycle 1 (D1C1), D1C5, D1C9, D1C13 (cycle length=14 days), end of study (EoS, within 28 to 42 days after last dose, latest at 29 months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the immunogenicity of Bevacizumab is already known and well characterized, no immunogenicity was evaluated for Bevacizumab.

End point values	Vanucizumab + mFOLFOX-6	Safety run-in (part 1)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	93	8		
Units: Number of Participants	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve (AUC) of Vanucizumab

End point title	Area Under the Plasma Concentration-Time Curve (AUC) of Vanucizumab[3]

End point description:

PK profile of vanucizumab was evaluated in terms of AUC, values are reported for cycle 8 of part 1 (safety run-in) and part 2 of the study.

End point type	Secondary

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered

Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

End point values	Vanucizumab + mFOLFOX-6	Safety run-in (part 1)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	3		
Units: hr*ug/ml				
geometric mean (geometric coefficient of variation)				
Cycle 8	82100 (± 31.6)	112000 (± 11.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Vanucizumab

End point title	Maximum Observed Plasma Concentration (Cmax) of Vanucizumab[4]

End point description:

PK profile of vanucizumab was evaluated in terms of Cmax, values are reported for cycle 8 for both part 1 (safety run-in) and part 2 of the study.

End point type	Secondary

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

End point values	Vanucizumab + mFOLFOX-6	Safety run-in (part 1)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	64	6		
Units: ug/ml				
geometric mean (geometric coefficient of variation)	794 (± 38.2)	685 (± 17.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Concentration (Clast) of Vanucizumab

End point title	Minimum Observed Plasma Concentration (Clast) of Vanucizumab[5]

End point description:

PK profile of vanucizumab was evaluated in terms of Clast, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

End point type	Secondary

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs]), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose), at PD/ EoS (latest at 29 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

End point values	Vanucizumab + mFOLFOX-6			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: ug/ml				
geometric mean (geometric coefficient of variation)				
Cycle 8	361 (± 39.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Cmax (Tmax) of Vanucizumab

End point title	Time to Reach Cmax (Tmax) of Vanucizumab[6]

End point description:

PK profile of vanucizumab was evaluated in terms of Tmax for cycles 8 for both part 1 (safety run-in) and part 2 of the study.

End point type	Secondary

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

End point values	Vanucizumab + mFOLFOX-6	Safety run-in (part 1)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	64	6		
Units: hr				
median (full range (min-max))				
Cycle 8	1.58 (0.5 to 4.77)	4.04 (0.5 to 5.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Terminal Half-Life (t1/2) of Vanucizumab

End point title	Plasma Terminal Half-Life (t1/2) of Vanucizumab[7]

End point description:

PK profile of vanucizumab was evaluated in terms of t1/2, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

End point type	Secondary

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

End point values	Vanucizumab + mFOLFOX-6	Safety run-in (part 1)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	37	3		
Units: hr				
geometric mean (geometric coefficient of variation)	157 (± 30.3)	202 (± 12.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Clearance at Steady State (CLss) of Vanucizumab

End point title	Plasma Clearance at Steady State (CLss) of Vanucizumab[8]

End point description:

PK profile of vanucizumab was evaluated in terms of CLss, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

End point type	Secondary

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

End point values	Vanucizumab + mFOLFOX-6	Safety run-in (part 1)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	37	3		
Units: ml/hr				
geometric mean (geometric coefficient of variation)	18 (± 29)	15.3 (± 26.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss) of Vanucizumab

End point title	Volume of Distribution at Steady State (Vss) of Vanucizumab[9]

End point description:

PK profile of vanucizumab was evaluated in terms of Vss, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

End point type	Secondary

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

End point values	Vanucizumab + mFOLFOX-6	Safety run-in (part 1)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	37	3		
Units: ml				
geometric mean (geometric coefficient of variation)	4140 (± 29.7)	4400 (± 25.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax Accumulation Ratio (AR) of Vanucizumab

End point title	Cmax Accumulation Ratio (AR) of Vanucizumab[10]

End point description:

PK profile of vanucizumab was evaluated in terms of Cmax Ratio, values are reported for cycle 8 of both part 1 (safety run-in) and part 2 of the study.

End point type	Secondary

End point timeframe:

Part 1 (C1, C6), Part 2 (C1, C8): D1 (Pre-dose [0 hrs], EoI [at 0.5-1.5 hrs], 1, 2, 4 hrs post infusion start), D2, D4, D6, D8 (cycle length=14 days); Part 1 (C2 to C5, C7 to C8), Part 2 (C2 to C7): D1 (pre-dose, EoI), at PD/ EoS (latest at 29 months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK end point was only evaluated in the arm where patients were administered Vanucizumab. Given that the PK of Bevacizumab with chemotherapy is already known and well characterized, no PK end point were evaluated for Bevacizumab.

End point values	Vanucizumab + mFOLFOX-6	Safety run-in (part 1)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	64	5		
Units: N/A				
geometric mean (geometric coefficient of variation)	1.63 (± 36.2)	1.51 (± 27.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 28 days after the last dose of study drug (maximum treatment time = approximately 29 months).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Vanucizumab + mFOLFOX-6

Reporting group description:

In the induction therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received vanucizumab at a dose of 2000 mg as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Reporting group title	Bevacizumab + mFOLFOX-6

Reporting group description:

In the induction therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; oxaliplatin at a dose of 85 mg/m^2 as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks for up to 8 cycles (approximately 4 months). Subsequently, in the maintenance therapy participants received bevacizumab at a dose of 5 milligram per kilogram (mg/kg) as IV infusion; folinic acid at a dose of 400 mg/m^2 as IV infusion; and 5-FU at a dose of 400 mg/m^2 as starting IV bolus followed by 2400 mg/m^2 as IV infusion every 2 weeks until disease progression, unacceptable toxicities, consent withdrawal or Investigator's decision for a maximum of 24 months.

Reporting group title	Safety run-in

Reporting group description:

8 eligible participants received 2000 milligrams (mg) vanucizumab + mFOLFOX-6 every two weeks for up to 8 cycles in order to confirm the dose and schedule for the overall study.

Serious adverse events	Vanucizumab + mFOLFOX-6	Bevacizumab + mFOLFOX-6	Safety run-in
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 93 (44.09%)	40 / 95 (42.11%)	3 / 8 (37.50%)
number of deaths (all causes)	16	21	3
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INFECTED NEOPLASM			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumor obstruction			

subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
AORTIC THROMBOSIS			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	2 / 93 (2.15%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASOSPASM			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLICATION ASSOCIATED WITH DEVICE			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			

subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON−CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 93 (4.30%)	4 / 95 (4.21%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
FEMALE GENITAL TRACT FISTULA			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPISTAXIS			

subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 93 (2.15%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
DEVICE DISLOCATION			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE OCCLUSION			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL ANASTOMOTIC LEAK			

subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC FRACTURE			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL FRACTURE			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorder			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Ischaemia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Guillain-Barre syndrome			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 93 (1.08%)	2 / 95 (2.11%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile Neutropenia			

subjects affected / exposed	0 / 93 (0.00%)	5 / 95 (5.26%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 93 (1.08%)	2 / 95 (2.11%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 93 (1.08%)	3 / 95 (3.16%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal ulcer			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 93 (1.08%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 93 (1.08%)	3 / 95 (3.16%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			

subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovesical fistula			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 93 (2.15%)	3 / 95 (3.16%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	3 / 93 (3.23%)	2 / 95 (2.11%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 93 (1.08%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	3 / 93 (3.23%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Nausea			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	3 / 93 (3.23%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILE DUCT STONE			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
CERVICAL SPINAL STENOSIS			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PATHOLOGICAL FRACTURE			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA INFECTIOUS			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOCCAL BACTERAEMIA			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 93 (0.00%)	2 / 95 (2.11%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 93 (0.00%)	2 / 95 (2.11%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Splenic abscess			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 93 (1.08%)	4 / 95 (4.21%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 93 (1.08%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FAILURE TO THRIVE			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Vanucizumab + mFOLFOX-6	Bevacizumab + mFOLFOX-6	Safety run-in
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 93 (96.77%)	94 / 95 (98.95%)	8 / 8 (100.00%)
Vascular disorders			
Embolism venous			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	41 / 93 (44.09%)	26 / 95 (27.37%)	5 / 8 (62.50%)
occurrences (all)	65	49	9
Hypotension			
subjects affected / exposed	0 / 93 (0.00%)	6 / 95 (6.32%)	1 / 8 (12.50%)
occurrences (all)	0	6	1
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	40 / 93 (43.01%)	42 / 95 (44.21%)	3 / 8 (37.50%)
occurrences (all)	90	127	6
Chest discomfort			
subjects affected / exposed	2 / 93 (2.15%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Chest pain			
subjects affected / exposed	5 / 93 (5.38%)	3 / 95 (3.16%)	0 / 8 (0.00%)
occurrences (all)	5	3	0
Fatigue			
subjects affected / exposed	26 / 93 (27.96%)	21 / 95 (22.11%)	1 / 8 (12.50%)
occurrences (all)	31	25	1
Mass			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	21 / 93 (22.58%)	31 / 95 (32.63%)	4 / 8 (50.00%)
occurrences (all)	40	66	6
Oedema peripheral			
subjects affected / exposed	10 / 93 (10.75%)	2 / 95 (2.11%)	3 / 8 (37.50%)
occurrences (all)	11	2	5
Pyrexia			
subjects affected / exposed	16 / 93 (17.20%)	15 / 95 (15.79%)	1 / 8 (12.50%)
occurrences (all)	22	21	1
Temperature intolerance			
subjects affected / exposed	11 / 93 (11.83%)	10 / 95 (10.53%)	1 / 8 (12.50%)
occurrences (all)	15	16	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 93 (10.75%)	9 / 95 (9.47%)	1 / 8 (12.50%)
occurrences (all)	12	12	1
Dysphonia			
subjects affected / exposed	12 / 93 (12.90%)	9 / 95 (9.47%)	1 / 8 (12.50%)
occurrences (all)	12	12	2
Dyspnoea			

subjects affected / exposed	10 / 93 (10.75%)	10 / 95 (10.53%)	1 / 8 (12.50%)
occurrences (all)	11	12	1
Epistaxis			
subjects affected / exposed	19 / 93 (20.43%)	28 / 95 (29.47%)	2 / 8 (25.00%)
occurrences (all)	26	36	2
Hiccups			
subjects affected / exposed	4 / 93 (4.30%)	2 / 95 (2.11%)	1 / 8 (12.50%)
occurrences (all)	4	3	1
OROPHARYNGEAL PAIN			
subjects affected / exposed	3 / 93 (3.23%)	6 / 95 (6.32%)	1 / 8 (12.50%)
occurrences (all)	3	6	1
Rhinorrhoea			
subjects affected / exposed	4 / 93 (4.30%)	5 / 95 (5.26%)	0 / 8 (0.00%)
occurrences (all)	5	5	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 93 (9.68%)	8 / 95 (8.42%)	1 / 8 (12.50%)
occurrences (all)	9	8	1
Depression			
subjects affected / exposed	6 / 93 (6.45%)	1 / 95 (1.05%)	1 / 8 (12.50%)
occurrences (all)	6	1	1
Insomnia			
subjects affected / exposed	11 / 93 (11.83%)	12 / 95 (12.63%)	0 / 8 (0.00%)
occurrences (all)	11	13	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 93 (3.23%)	5 / 95 (5.26%)	0 / 8 (0.00%)
occurrences (all)	4	5	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 93 (3.23%)	7 / 95 (7.37%)	0 / 8 (0.00%)
occurrences (all)	7	7	0
GAMMA−GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	1 / 93 (1.08%)	4 / 95 (4.21%)	1 / 8 (12.50%)
occurrences (all)	1	5	1
Lipase increased			

subjects affected / exposed	2 / 93 (2.15%)	8 / 95 (8.42%)	0 / 8 (0.00%)
occurrences (all)	2	8	0
Platelet count decreased			
subjects affected / exposed	10 / 93 (10.75%)	4 / 95 (4.21%)	0 / 8 (0.00%)
occurrences (all)	25	6	0
Weight decreased			
subjects affected / exposed	11 / 93 (11.83%)	13 / 95 (13.68%)	0 / 8 (0.00%)
occurrences (all)	12	13	0
Weight increased			
subjects affected / exposed	4 / 93 (4.30%)	2 / 95 (2.11%)	1 / 8 (12.50%)
occurrences (all)	4	2	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 93 (3.23%)	3 / 95 (3.16%)	1 / 8 (12.50%)
occurrences (all)	4	3	2
Infusion related reaction			
subjects affected / exposed	19 / 93 (20.43%)	12 / 95 (12.63%)	1 / 8 (12.50%)
occurrences (all)	26	17	1
Nervous system disorders			
Aphonia			
subjects affected / exposed	5 / 93 (5.38%)	2 / 95 (2.11%)	0 / 8 (0.00%)
occurrences (all)	5	2	0
Dizziness			
subjects affected / exposed	10 / 93 (10.75%)	12 / 95 (12.63%)	1 / 8 (12.50%)
occurrences (all)	12	17	1
Dysaesthesia			
subjects affected / exposed	15 / 93 (16.13%)	22 / 95 (23.16%)	1 / 8 (12.50%)
occurrences (all)	32	79	3
Dysgeusia			
subjects affected / exposed	16 / 93 (17.20%)	22 / 95 (23.16%)	5 / 8 (62.50%)
occurrences (all)	16	26	6
Headache			
subjects affected / exposed	15 / 93 (16.13%)	18 / 95 (18.95%)	2 / 8 (25.00%)
occurrences (all)	16	29	2
Hypoaesthesia			

subjects affected / exposed	0 / 93 (0.00%)	3 / 95 (3.16%)	1 / 8 (12.50%)
occurrences (all)	0	3	2
Neuropathy peripheral			
subjects affected / exposed	16 / 93 (17.20%)	26 / 95 (27.37%)	3 / 8 (37.50%)
occurrences (all)	29	62	8
Neurotoxicity			
subjects affected / exposed	8 / 93 (8.60%)	2 / 95 (2.11%)	0 / 8 (0.00%)
occurrences (all)	14	2	0
Paraesthesia			
subjects affected / exposed	15 / 93 (16.13%)	17 / 95 (17.89%)	1 / 8 (12.50%)
occurrences (all)	17	24	1
Peripheral sensory neuropathy			
subjects affected / exposed	32 / 93 (34.41%)	27 / 95 (28.42%)	2 / 8 (25.00%)
occurrences (all)	79	70	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 93 (6.45%)	12 / 95 (12.63%)	3 / 8 (37.50%)
occurrences (all)	7	19	3
Leukopenia			
subjects affected / exposed	1 / 93 (1.08%)	3 / 95 (3.16%)	1 / 8 (12.50%)
occurrences (all)	1	3	1
Neutropenia			
subjects affected / exposed	39 / 93 (41.94%)	42 / 95 (44.21%)	4 / 8 (50.00%)
occurrences (all)	52	63	6
Thrombocytopenia			
subjects affected / exposed	4 / 93 (4.30%)	8 / 95 (8.42%)	3 / 8 (37.50%)
occurrences (all)	6	8	4
Eye disorders			
Cataract			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Eyelid oedema			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Lacrimation increase			

subjects affected / exposed	4 / 93 (4.30%)	5 / 95 (5.26%)	2 / 8 (25.00%)
occurrences (all)	5	6	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	26 / 93 (27.96%)	18 / 95 (18.95%)	2 / 8 (25.00%)
occurrences (all)	33	19	3
Abdominal pain lower			
subjects affected / exposed	7 / 93 (7.53%)	3 / 95 (3.16%)	0 / 8 (0.00%)
occurrences (all)	8	3	0
Abdominal pain upper			
subjects affected / exposed	6 / 93 (6.45%)	12 / 95 (12.63%)	0 / 8 (0.00%)
occurrences (all)	9	12	0
Constipation			
subjects affected / exposed	24 / 93 (25.81%)	29 / 95 (30.53%)	3 / 8 (37.50%)
occurrences (all)	35	48	5
Diarrhoea			
subjects affected / exposed	54 / 93 (58.06%)	54 / 95 (56.84%)	6 / 8 (75.00%)
occurrences (all)	102	127	8
Dry mouth			
subjects affected / exposed	4 / 93 (4.30%)	5 / 95 (5.26%)	0 / 8 (0.00%)
occurrences (all)	4	6	0
Dyspepsia			
subjects affected / exposed	11 / 93 (11.83%)	8 / 95 (8.42%)	0 / 8 (0.00%)
occurrences (all)	14	12	0
Flatulence			
subjects affected / exposed	5 / 93 (5.38%)	2 / 95 (2.11%)	0 / 8 (0.00%)
occurrences (all)	6	2	0
Gingival bleeding			
subjects affected / exposed	0 / 93 (0.00%)	3 / 95 (3.16%)	1 / 8 (12.50%)
occurrences (all)	0	3	1
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypoaesthesia oral			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Nausea			
subjects affected / exposed	51 / 93 (54.84%)	55 / 95 (57.89%)	6 / 8 (75.00%)
occurrences (all)	90	98	6
Odynophagia			
subjects affected / exposed	2 / 93 (2.15%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Oral pain			
subjects affected / exposed	6 / 93 (6.45%)	1 / 95 (1.05%)	0 / 8 (0.00%)
occurrences (all)	6	1	0
Proctalgia			
subjects affected / exposed	1 / 93 (1.08%)	3 / 95 (3.16%)	1 / 8 (12.50%)
occurrences (all)	2	4	1
Rectal haemorrhage			
subjects affected / exposed	3 / 93 (3.23%)	4 / 95 (4.21%)	1 / 8 (12.50%)
occurrences (all)	3	4	1
Stomatitis			
subjects affected / exposed	15 / 93 (16.13%)	11 / 95 (11.58%)	1 / 8 (12.50%)
occurrences (all)	23	15	1
Vomiting			
subjects affected / exposed	29 / 93 (31.18%)	27 / 95 (28.42%)	1 / 8 (12.50%)
occurrences (all)	39	45	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 93 (5.38%)	14 / 95 (14.74%)	1 / 8 (12.50%)
occurrences (all)	5	14	1
Nail disorder			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
PALMAR−PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	7 / 93 (7.53%)	15 / 95 (15.79%)	2 / 8 (25.00%)
occurrences (all)	12	21	2
Rash			
subjects affected / exposed	5 / 93 (5.38%)	8 / 95 (8.42%)	0 / 8 (0.00%)
occurrences (all)	8	10	0
Skin hyperpigmentation			

subjects affected / exposed	4 / 93 (4.30%)	4 / 95 (4.21%)	2 / 8 (25.00%)
occurrences (all)	5	5	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	5 / 93 (5.38%)	6 / 95 (6.32%)	0 / 8 (0.00%)
occurrences (all)	5	8	0
Proteinuria			
subjects affected / exposed	11 / 93 (11.83%)	9 / 95 (9.47%)	1 / 8 (12.50%)
occurrences (all)	14	15	5
Urinary tract pain			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 93 (4.30%)	8 / 95 (8.42%)	2 / 8 (25.00%)
occurrences (all)	4	10	4
Back pain			
subjects affected / exposed	8 / 93 (8.60%)	14 / 95 (14.74%)	1 / 8 (12.50%)
occurrences (all)	9	16	1
Bone pain			
subjects affected / exposed	1 / 93 (1.08%)	5 / 95 (5.26%)	1 / 8 (12.50%)
occurrences (all)	1	6	2
Musculoskeletal pain			
subjects affected / exposed	9 / 93 (9.68%)	7 / 95 (7.37%)	1 / 8 (12.50%)
occurrences (all)	12	9	1
Myalgia			
subjects affected / exposed	8 / 93 (8.60%)	7 / 95 (7.37%)	0 / 8 (0.00%)
occurrences (all)	11	10	0
Pain in extremitiy			
subjects affected / exposed	2 / 93 (2.15%)	6 / 95 (6.32%)	2 / 8 (25.00%)
occurrences (all)	2	7	2
Pain in jaw			
subjects affected / exposed	6 / 93 (6.45%)	2 / 95 (2.11%)	0 / 8 (0.00%)
occurrences (all)	6	4	0
Infections and infestations			

Ear infection			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Furuncle			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	4 / 93 (4.30%)	2 / 95 (2.11%)	1 / 8 (12.50%)
occurrences (all)	4	3	1
Nasopharyngitis			
subjects affected / exposed	7 / 93 (7.53%)	8 / 95 (8.42%)	2 / 8 (25.00%)
occurrences (all)	8	11	2
Oral candidiasis			
subjects affected / exposed	5 / 93 (5.38%)	1 / 95 (1.05%)	1 / 8 (12.50%)
occurrences (all)	5	2	1
Periodontitis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 93 (0.00%)	3 / 95 (3.16%)	1 / 8 (12.50%)
occurrences (all)	0	3	2
Sinusitis			
subjects affected / exposed	3 / 93 (3.23%)	1 / 95 (1.05%)	1 / 8 (12.50%)
occurrences (all)	4	1	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 93 (2.15%)	13 / 95 (13.68%)	1 / 8 (12.50%)
occurrences (all)	2	14	1
Urinary tract infection			
subjects affected / exposed	10 / 93 (10.75%)	10 / 95 (10.53%)	2 / 8 (25.00%)
occurrences (all)	11	13	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	28 / 93 (30.11%)	32 / 95 (33.68%)	1 / 8 (12.50%)
occurrences (all)	44	66	3
Dehydration			

subjects affected / exposed	8 / 93 (8.60%)	7 / 95 (7.37%)	1 / 8 (12.50%)
occurrences (all)	10	7	1
Hyperglycaemia			
subjects affected / exposed	0 / 93 (0.00%)	6 / 95 (6.32%)	0 / 8 (0.00%)
occurrences (all)	0	10	0
Hyperuricaemia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 95 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	8 / 93 (8.60%)	10 / 95 (10.53%)	0 / 8 (0.00%)
occurrences (all)	9	10	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2014	Amended due to FDA request • An exclusion criterion for metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses of large volume, was added. • An exclusion criterion for history of gross hemoptysis (defined as bright red blood or ≥ 1/2 teaspoon) within 2 months prior to randomization was added. • Further vanucizumab pharmacokinetic (PK) samples were added in Cycle 1 and Cycle 8.
16 May 2014	Amended due to request following VHP in Europe • For the Part I safety run-in, simultaneous (i.e., same day) treatment administration to several patients, for the first 6 patients, was no longer allowed. Treatment of the first 6 patients was sequential i.e., there was always at least 1 working day between the first vanucizumab administration of one enrolled patient and the first vanucizumab administration of the next enrolled patient.
10 June 2014	• The revisions in Protocol Version 2 (EU) and Protocol Version 1 (US) were combined into a harmonized Version 3.
08 September 2015	• The sample size was increased from 140 patients to approximately 190 patients in order to compensate for early patient discontinuations and thereby to ensure that the number of PFS events required for the core analysis (n = 80) would be reached.
10 February 2016	• Risk mitigation measures were implemented as described in the Dear Investigator Letter (DIL) of 24 December 2015. The reason for submission of the DIL was to inform investigators that 10% of patients across two studies with vanucizumab had experienced gastrointestinal (GI) perforations (including GI fistula and intra abdominal abscess) and to inform them about additional risk mitigation measures that were made effective immediately to ensure the utmost safety and well- being of the patients, including: – Re-consenting ongoing patients to inform them about the increased risk of GI perforation associated with the blinded study drug treatment. – Excluding patients with a history of peptic ulcer disease, diverticulitis, or colitis within 6 months prior to Day 1 of Cycle 1. – Excluding patients with abdominal surgery or interventions within 60 days prior to Day 1 of Cycle 1. – Excluding patients with colonic prosthesis (stent) implant in place. – Permanently discontinuing study drug treatment in patients with confirmed intestinal sub-occlusive syndrome/occlusive syndrome/intestinal obstruction. – Advising patients to immediately contact the study physician in case they experience clinical symptoms suggestive of intestinal sub-/occlusion/intestinal obstruction or GI perforation such as acute, persisting and/or increasing abdominal pain, nausea and vomiting, etc. in order to initiate the appropriate diagnostic and therapeutic measures for this condition. – Prohibiting concomitant chronic use of non steroidal anti inflammatory drugs (NSAIDs) while receiving study drugs. However, for the symptomatic relief of medical conditions (e.g. headache, fever) sporadic or short-term intake of oral NSAIDs was allowed, when co-administered with proton pump inhibitors to reduce potential gastrointestinal damage.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported