Clinical trial results:
A prospective, randomized Phase III trial of carboplatin/gemcitabine/bevacizumab vs. carboplatin/pegylated liposomal doxorubicin/bevacizumab in patients with platinum-sensitive recurrent ovarian cancer.

Summary

EudraCT number	2012-004125-24
Trial protocol	DE AT BE GB
Global end of trial date	19 January 2021

Results information

Result version number	v1 (current)
This version publication date	30 July 2022
First version publication date	30 July 2022

Trial information

Trial identification

Sponsor protocol code	AGO-OVAR2.21

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01837251
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AGO Research GmbH
Sponsor organisation address	Kaiser-Friedrich-Ring 71, Wiesbaden, Germany, 65185
Public contact	Study Office, AGO Research GmbH, 0049 6118804670, office-wiesbaden@ago-ovar.de
Scientific contact	Study Office, AGO Research GmbH, 0049 6118804670, office-wiesbaden@ago-ovar.de

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	01 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy outcome measure is investigator-determined progression-free survival (PFS)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	01 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	France: 107
Country: Number of subjects enrolled	Germany: 473
Country: Number of subjects enrolled	Australia: 76
Worldwide total number of subjects	682
EEA total number of subjects	599

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)	394
From 65 to 84 years	287
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

FPFV: 21-AUG-2013, LPLV: 14-JAN-2019

Pre-assignment

Screening details:

The study consisted of a screening/baseline period, a treatment period and a posttreatment or follow-up period.

Period 1

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

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 2 (experimental group)

Arm description:

Bevacizumab, Peylated Liposomal Doxorubicin, Carboplatin

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

Dosage and administration details:

15mg/kg/body weight

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10mg/kg/body weight

Arm title	Arm 1 (standard group)

Arm description:

Bevacizumab, Gemcitabine, Carboplatin

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

Dosage and administration details:

15mg/kg/body weight

Number of subjects in period 1	Arm 2 (experimental group)	Arm 1 (standard group)
Started	345	337
Completed	332	329
Not completed	13	8
did not receive allocated intervention	8	5
received only chemotherapy	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Arm 2 (experimental group)
Reporting group description: Bevacizumab, Peylated Liposomal Doxorubicin, Carboplatin	
Reporting group title	Arm 1 (standard group)
Reporting group description: Bevacizumab, Gemcitabine, Carboplatin	

Reporting group values	Arm 2 (experimental group)	Arm 1 (standard group)	Total
Number of subjects	345	337	682
Age categorical			
female patients 18 years and older.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	202	192	394
From 65-84 years	143	144	287
85 years and over	0	1	1
Gender categorical Units: Subjects			
Female	345	337	682
Male	0	0	0

End points

End points reporting groups

Reporting group title	Arm 2 (experimental group)
Reporting group description: Bevacizumab, Peylated Liposomal Doxorubicin, Carboplatin	
Reporting group title	Arm 1 (standard group)
Reporting group description: Bevacizumab, Gemcitabine, Carboplatin	

Primary: Progression free survival

End point title	Progression free survival
End point description:	
End point type	Primary
End point timeframe: PFS defined as the interval between randomisation and first documented disease progression or death, whichever occurred first	

End point values	Arm 2 (experimental group)	Arm 1 (standard group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332	329		
Units: months				
number (not applicable)	13.3	11.6		

Statistical analyses

Statistical analysis title	Primary statistical analysis
Statistical analysis description: Efficacy outcomes were analysed in the intention-to-treat population, defined as all randomly assigned patients irrespective of whether they actually received treatment. Progression-free survival were compared between the two treatment groups using a stratified log-rank test at a two-sided 5% significance level, stratified by the factors used for randomisation. Median progression-free survival were estimated using Kaplan-Meier estimates with corresponding 95% CIs.	
Comparison groups	Arm 2 (experimental group) v Arm 1 (standard group)

Number of subjects included in analysis	661
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Logrank

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Events occurring during the clinical trial or within 30 days after treatment discontinuation	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Arm 2
Reporting group description:	
Experimental group: Bevacizumab, Peylated Liposomal Doxorubicin, Carboplatin	
Reporting group title	Arm 1
Reporting group description:	
Standard group: Bevacizumab, Gemcitabine, Carboplatin	

Serious adverse events	Arm 2	Arm 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 332 (9.94%)	28 / 329 (8.51%)	
number of deaths (all causes)	207	232	
number of deaths resulting from adverse events	13	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			

subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thyroid cancer			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial stenosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 332 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			

subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	11 / 332 (3.31%)	4 / 329 (1.22%)	
occurrences causally related to treatment / all	13 / 13	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	4 / 332 (1.20%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheter management			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation venous			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			

subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implantable pleural catheter insertion			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenectomy			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrostomy			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 332 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 332 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			

subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 332 (0.90%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	14 / 332 (4.22%)	16 / 329 (4.86%)	
occurrences causally related to treatment / all	3 / 20	4 / 20	
deaths causally related to treatment / all	2 / 2	2 / 2	
Impaired healing			
subjects affected / exposed	1 / 332 (0.30%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	1 / 117	1 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 332 (0.00%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 332 (1.20%)	7 / 329 (2.13%)	
occurrences causally related to treatment / all	0 / 5	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 332 (0.00%)	9 / 329 (2.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 332 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 332 (1.51%)	5 / 329 (1.52%)	
occurrences causally related to treatment / all	2 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 332 (0.60%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	9 / 332 (2.71%)	6 / 329 (1.82%)	
occurrences causally related to treatment / all	0 / 13	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 332 (1.51%)	5 / 329 (1.52%)	
occurrences causally related to treatment / all	5 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood altered			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematology test abnormal			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 332 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	8 / 332 (2.41%)	10 / 329 (3.04%)	
occurrences causally related to treatment / all	6 / 9	3 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis complication			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax traumatic			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urostomy complication			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			

subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 332 (0.90%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiotoxicity			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	2 / 332 (0.60%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 332 (0.30%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 332 (0.60%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	2 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			

subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osmotic demyelination syndrome			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Parkinsonism			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 332 (0.30%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 332 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	4 / 332 (1.20%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	9 / 332 (2.71%)	8 / 329 (2.43%)	
occurrences causally related to treatment / all	3 / 12	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood disorder			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 332 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematotoxicity			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 332 (0.30%)	6 / 329 (1.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	4 / 332 (1.20%)	6 / 329 (1.82%)	
occurrences causally related to treatment / all	1 / 4	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			

subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	7 / 332 (2.11%)	25 / 329 (7.60%)	
occurrences causally related to treatment / all	5 / 10	8 / 32	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 332 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	13 / 332 (3.92%)	12 / 329 (3.65%)	
occurrences causally related to treatment / all	4 / 13	6 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal strangulated hernia			

subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 332 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 332 (0.90%)	8 / 329 (2.43%)	
occurrences causally related to treatment / all	1 / 4	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	5 / 332 (1.51%)	4 / 329 (1.22%)	
occurrences causally related to treatment / all	3 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	2 / 332 (0.60%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faeces discoloured			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 332 (0.30%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	8 / 332 (2.41%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	4 / 9	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	4 / 332 (1.20%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal perforation			
subjects affected / exposed	2 / 332 (0.60%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nausea			
subjects affected / exposed	9 / 332 (2.71%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	3 / 9	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			

subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 332 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	13 / 332 (3.92%)	8 / 329 (2.43%)	
occurrences causally related to treatment / all	4 / 18	4 / 10	
deaths causally related to treatment / all	2 / 2	0 / 0	
Vomiting			
subjects affected / exposed	9 / 332 (2.71%)	8 / 329 (2.43%)	
occurrences causally related to treatment / all	6 / 11	0 / 9	
deaths causally related to treatment / all	1 / 1	0 / 1	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Haemorrhage subcutaneous			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 332 (0.30%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 332 (0.30%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nephrotic syndrome			
subjects affected / exposed	2 / 332 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	5 / 332 (1.51%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	3 / 332 (0.90%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal haemorrhage			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary fistula			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			

subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 332 (0.30%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Anal abscess			
subjects affected / exposed	2 / 332 (0.60%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	3 / 332 (0.90%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fascioliasis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	2 / 332 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	6 / 332 (1.81%)	4 / 329 (1.22%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Influenza			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharingitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 332 (0.30%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	2 / 332 (0.60%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	5 / 332 (1.51%)	9 / 329 (2.74%)	
occurrences causally related to treatment / all	1 / 5	3 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 332 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 332 (0.60%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 332 (0.60%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 332 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Malnutrition			
subjects affected / exposed	0 / 332 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm 2	Arm 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	327 / 332 (98.49%)	319 / 329 (96.96%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	144 / 332 (43.37%)	121 / 329 (36.78%)	
occurrences (all)	502	399	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	23 / 332 (6.93%)	31 / 329 (9.42%)	
occurrences (all)	69	59	
Fatigue			
subjects affected / exposed	163 / 332 (49.10%)	147 / 329 (44.68%)	
occurrences (all)	343	281	
Mucosal inflammation			
subjects affected / exposed	59 / 332 (17.77%)	38 / 329 (11.55%)	
occurrences (all)	117	57	
Oedema			
subjects affected / exposed	18 / 332 (5.42%)	0 / 329 (0.00%)	
occurrences (all)	31	0	
Oedema peripheral			
subjects affected / exposed	30 / 332 (9.04%)	27 / 329 (8.21%)	
occurrences (all)	38	40	
Pain			
subjects affected / exposed	22 / 332 (6.63%)	0 / 329 (0.00%)	
occurrences (all)	47	0	
Pyrexia			
subjects affected / exposed	23 / 332 (6.93%)	22 / 329 (6.69%)	
occurrences (all)	32	26	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 332 (7.83%)	23 / 329 (6.99%)	
occurrences (all)	32	27	
Dysphonia			

subjects affected / exposed	17 / 332 (5.12%)	0 / 329 (0.00%)	
occurrences (all)	22	0	
Dyspnoea			
subjects affected / exposed	71 / 332 (21.39%)	61 / 329 (18.54%)	
occurrences (all)	114	90	
Epistaxis			
subjects affected / exposed	80 / 332 (24.10%)	82 / 329 (24.92%)	
occurrences (all)	112	113	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 332 (0.00%)	19 / 329 (5.78%)	
occurrences (all)	0	21	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	34 / 332 (10.24%)	50 / 329 (15.20%)	
occurrences (all)	131	168	
Platelet count decreased			
subjects affected / exposed	52 / 332 (15.66%)	53 / 329 (16.11%)	
occurrences (all)	231	172	
White blood cell count decreased			
subjects affected / exposed	19 / 332 (5.72%)	34 / 329 (10.33%)	
occurrences (all)	65	113	
Nervous system disorders			
Dizziness			
subjects affected / exposed	27 / 332 (8.13%)	21 / 329 (6.38%)	
occurrences (all)	32	33	
Dysgeusia			
subjects affected / exposed	32 / 332 (9.64%)	21 / 329 (6.38%)	
occurrences (all)	39	22	
Headache			
subjects affected / exposed	82 / 332 (24.70%)	71 / 329 (21.58%)	
occurrences (all)	155	125	
Peripheral sensory neuropathy			
subjects affected / exposed	39 / 332 (11.75%)	34 / 329 (10.33%)	
occurrences (all)	57	48	
Polyneuropathy			

subjects affected / exposed	23 / 332 (6.93%)	0 / 329 (0.00%)	
occurrences (all)	34	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	121 / 332 (36.45%)	132 / 329 (40.12%)	
occurrences (all)	463	441	
Leukopenia			
subjects affected / exposed	29 / 332 (8.73%)	45 / 329 (13.68%)	
occurrences (all)	88	152	
Neutropenia			
subjects affected / exposed	59 / 332 (17.77%)	102 / 329 (31.00%)	
occurrences (all)	209	355	
Thrombocytopenia			
subjects affected / exposed	61 / 332 (18.37%)	93 / 329 (28.27%)	
occurrences (all)	215	286	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	17 / 332 (5.12%)	0 / 329 (0.00%)	
occurrences (all)	26	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	45 / 332 (13.55%)	56 / 329 (17.02%)	
occurrences (all)	65	100	
Abdominal pain upper			
subjects affected / exposed	33 / 332 (9.94%)	22 / 329 (6.69%)	
occurrences (all)	48	32	
Constipation			
subjects affected / exposed	111 / 332 (33.43%)	109 / 329 (33.13%)	
occurrences (all)	169	161	
Diarrhoea			
subjects affected / exposed	82 / 332 (24.70%)	68 / 329 (20.67%)	
occurrences (all)	176	124	
Nausea			
subjects affected / exposed	168 / 332 (50.60%)	176 / 329 (53.50%)	
occurrences (all)	352	354	
Stomatitis			

subjects affected / exposed	56 / 332 (16.87%)	42 / 329 (12.77%)	
occurrences (all)	96	78	
Vomiting			
subjects affected / exposed	88 / 332 (26.51%)	78 / 329 (23.71%)	
occurrences (all)	148	115	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	59 / 332 (17.77%)	82 / 329 (24.92%)	
occurrences (all)	64	104	
Dry skin			
subjects affected / exposed	22 / 332 (6.63%)	0 / 329 (0.00%)	
occurrences (all)	30	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	65 / 332 (19.58%)	0 / 329 (0.00%)	
occurrences (all)	127	0	
Rash			
subjects affected / exposed	32 / 332 (9.64%)	21 / 329 (6.38%)	
occurrences (all)	46	30	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	75 / 332 (22.59%)	70 / 329 (21.28%)	
occurrences (all)	286	209	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	42 / 332 (12.65%)	37 / 329 (11.25%)	
occurrences (all)	55	49	
Back pain			
subjects affected / exposed	23 / 332 (6.93%)	43 / 329 (13.07%)	
occurrences (all)	29	64	
Myalgia			
subjects affected / exposed	27 / 332 (8.13%)	17 / 329 (5.17%)	
occurrences (all)	31	33	
Pain in extremity			
subjects affected / exposed	19 / 332 (5.72%)	28 / 329 (8.51%)	
occurrences (all)	27	33	
Infections and infestations			

Cystitis			
subjects affected / exposed	17 / 332 (5.12%)	18 / 329 (5.47%)	
occurrences (all)	24	27	
Nasopharyngitis			
subjects affected / exposed	35 / 332 (10.54%)	30 / 329 (9.12%)	
occurrences (all)	48	43	
Rhinitis			
subjects affected / exposed	18 / 332 (5.42%)	0 / 329 (0.00%)	
occurrences (all)	20	0	
Urinary tract infection			
subjects affected / exposed	47 / 332 (14.16%)	51 / 329 (15.50%)	
occurrences (all)	71	72	
Blood creatinine increased			
subjects affected / exposed	29 / 332 (8.73%)	0 / 329 (0.00%)	
occurrences (all)	77	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	38 / 332 (11.45%)	25 / 329 (7.60%)	
occurrences (all)	51	37	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2013	- Amendment 1 (Protocol V1.1F of 19-MAR-2013 Non-inferiority study design was changed into a superiority study design. The rationale has been adapted to the new design. The resulting new sample size estimation (enrolment of 654 instead of 870 patients (327 instead of 435 per arm)) arose out of considerations which minimum clinically relevant effect has to be evidenced in the experimental arm to justify the rationale in consideration of a similar safety profiles in both arms. Inclusion/exclusion criteria have been amended. Specific quantitative and qualitative criteria for termination of the trial have been added
05 April 2013	- Amendment 2 (Protocol V1.2F of 05-APR-2013): upper limit for blood pressure blood pressure was lowered to systolic <= 140 mmHg and diastolic <= 90 mmHg.
23 February 2015	- Amendment 4 (Protocol V02F of 20-FEB-2015): In the reformatted Section 6, biomarker data are not longer presented as these are not considered relevant to investigators when making therapeutic decisions. The biomarker data presented in Section 5 remains in this Investigator's Brochure. There have been no changes in the identified risks associated with the use of bevacizumab with the exception that embryofetal development disturbance is now considered an identified risk.
22 March 2016	- Amendment 6 (Protocol V03F of 22-MAR-2016): Protocol V03F contains substantial changes regarding the address of the coordinating investigator (LKP), changes for the post treatment follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32305099