Clinical trial results:
A Phase II-III Randomized Trial of Pemetrexed-Cisplatin Chemotherapy With or Without Bevacizumab (Avastin), 15 mg/kg, for Malignant Pleural Mesothelioma

Summary

EudraCT number	2007-002574-63
Trial protocol	FR
Global end of trial date	31 July 2016

Results information

Result version number	v1 (current)
This version publication date	16 April 2021
First version publication date	16 April 2021

Trial information

Trial identification

Sponsor protocol code	IFCT-0701

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00651456
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IFCT
Sponsor organisation address	10 rue de la Grange-Batelière, Paris, France, 75009
Public contact	Responsable communication, IFCT, contact@ifct.fr
Scientific contact	Responsable communication, IFCT, 33 0156811046, contact@ifct.fr

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	15 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Overall survival

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2008
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	France: 448
Worldwide total number of subjects	448
EEA total number of subjects	448

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)	204
From 65 to 84 years	244
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients included in this study were recruited in 73 sites located in France from February 2008 until July 2016.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	448
Number of subjects completed	448

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Chemotherapy (Arm A)

Arm description:

Standard Chemotherapy (Pemetrexed and Cisplatin)
Pemetrexed 500 mg/m² with previous Folic acid and vitamin B12 supplementation Day 1 (D1=D22, 6 cycles)
Cisplatin 75 mg/m² Day 1 (D1=D22, 6 cycles)

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

Dosage and administration details:

Pemetrexed 500 mg/m² with previous Folic acid and vitamin B12 supplementation Day 1 (D1=D22, 6 cycles)

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

Dosage and administration details:

Cisplatin 75 mg/m² Day 1 (D1=D22, 6 cycles)

Arm title	Standard Chemotherapy + bevacizumab (Arm B)

Arm description:

Standard Chemotherapy (Pemetrexed and Cisplatin) + Bevacizumab
Pemetrexed 500 mg/m² with previous Folic acid and vitamin B12 supplementation D1 (D1=D22, 6 cycles)
Cisplatin 75 mg/m2 D1 (D1=D22, 6 cycles)
Bevacizumab 15 mg/kg D1 (D1=D22, until progression)

Arm type	Experimental

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

Dosage and administration details:

Cisplatin 75 mg/m2 D1 (D1=D22, 6 cycles)

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

Dosage and administration details:

Pemetrexed 500 mg/m² with previous Folic acid and vitamin B12 supplementation D1 (D1=D22, 6 cycles)

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

Dosage and administration details:

Bevacizumab 15 mg/kg D1 (D1=D22, until progression)

Number of subjects in period 1	Standard Chemotherapy (Arm A)	Standard Chemotherapy + bevacizumab (Arm B)
Started	225	223
Completed	221	220
Not completed	4	3
Not eligible	-	3
Not eligible patient	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Standard Chemotherapy (Arm A)
Reporting group description:	
Standard Chemotherapy (Pemetrexed and Cisplatin) Pemetrexed 500 mg/m² with previous Folic acid and vitamin B12 supplementation Day 1 (D1=D22, 6 cycles) Cisplatin 75 mg/m² Day 1 (D1=D22, 6 cycles)	
Reporting group title	Standard Chemotherapy + bevacizumab (Arm B)
Reporting group description:	
Standard Chemotherapy (Pemetrexed and Cisplatin) + Bevacizumab Pemetrexed 500 mg/m² with previous Folic acid and vitamin B12 supplementation D1 (D1=D22, 6 cycles) Cisplatin 75 mg/m2 D1 (D1=D22, 6 cycles) Bevacizumab 15 mg/kg D1 (D1=D22, until progression)	

Reporting group values	Standard Chemotherapy (Arm A)	Standard Chemotherapy + bevacizumab (Arm B)	Total
Number of subjects	225	223	448
Age categorical Units: Subjects			
Adults (18-64 years)	97	107	204
From 65-84 years	128	116	244
Age continuous Units: years			
median	65.6	65.7	
full range (min-max)	34.7 to 75.9	38.5 to 75.8	-
Gender categorical Units: Subjects			
Female	55	55	110
Male	170	168	338
Histology Units: Subjects			
Epithelioid	182	179	361
Sarcomatoid-mixed	43	44	87
ECOG PS Units: Subjects			
0-1	217	216	433
≥2	8	7	15
Smoking status Units: Subjects			
Smoker	129	125	254
Never smoker	96	98	194
Leucocytes Units: Subjects			
<8·3 ×109/L	124	132	256
≥8·3 ×109/L	101	91	192
Haemoglobin Units: Subjects			

>14 g/dL	65	74	139
≤14 g/dL	160	149	309
Platelets Units: Subjects			
<400 ×109/L	164	172	336
≥400 ×109/L	61	51	112
Thoracoscopy Units: Subjects			
Yes	189	193	382
No	36	30	66
Weight loss Units: percentage			
arithmetic mean	5.4	5.4	
standard deviation	± 3.1	± 2.9	-

End points

End points reporting groups

Reporting group title	Standard Chemotherapy (Arm A)
Reporting group description:	
Standard Chemotherapy (Pemetrexed and Cisplatin) Pemetrexed 500 mg/m² with previous Folic acid and vitamin B12 supplementation Day 1 (D1=D22, 6 cycles) Cisplatin 75 mg/m² Day 1 (D1=D22, 6 cycles)	
Reporting group title	Standard Chemotherapy + bevacizumab (Arm B)
Reporting group description:	
Standard Chemotherapy (Pemetrexed and Cisplatin) + Bevacizumab Pemetrexed 500 mg/m² with previous Folic acid and vitamin B12 supplementation D1 (D1=D22, 6 cycles) Cisplatin 75 mg/m2 D1 (D1=D22, 6 cycles) Bevacizumab 15 mg/kg D1 (D1=D22, until progression)	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients who received at least one protocol treatment	
Subject analysis set title	Eligible population
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients without deviation at inclusion.	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
all population	

Primary: Overall survival

End point title	Overall survival
End point description:	
End point type	Primary
End point timeframe:	
The duration of overall survival is defined as the time elapsed between the date of randomization and death. If the patient does not die, survival will be censored at the given date or the date of the last results. The mediane follow-up was 39.4 months.	

End point values	Standard Chemotherapy (Arm A)	Standard Chemotherapy + bevacizumab (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	223		
Units: months				
median (confidence interval 95%)	16.1 (14.0 to 17.9)	18.8 (15.9 to 22.6)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Standard Chemotherapy (Arm A) v Standard Chemotherapy + bevacizumab (Arm B)
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0167
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.95

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Secondary

End point timeframe:

Progression-free survival is defined as the time elapsed between randomization until the date of the first observation of progression or death (from any cause).

End point values	Standard Chemotherapy (Arm A)	Standard Chemotherapy + bevacizumab (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	223		
Units: months				
median (full range (min-max))	7.3 (6.7 to 8.0)	9.2 (8.5 to 10.5)		

Statistical analyses

Statistical analysis title	Progression-free survival
Comparison groups	Standard Chemotherapy (Arm A) v Standard Chemotherapy + bevacizumab (Arm B)
Number of subjects included in analysis	448
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.75

Secondary: Time to Progression

End point title	Time to Progression

End point description:

End point type	Secondary

End point timeframe:

Time to progression (TTP) is a related endpoint defined as the time from randomization to tumor progression explicitly.

End point values	Standard Chemotherapy (Arm A)	Standard Chemotherapy + bevacizumab (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	218		
Units: months				
number (not applicable)	189	137		

Statistical analyses

Statistical analysis title	Time to Progression
Comparison groups	Standard Chemotherapy (Arm A) v Standard Chemotherapy + bevacizumab (Arm B)

Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Secondary: EORTC QLQ C30 quality of life scores

End point title	EORTC QLQ C30 quality of life scores

End point description:

End point type	Secondary

End point timeframe:

For QLQ-C30 scores, we qualifi ed QoL as improved when we noted a ten point increase or greater for functioning scales and a ten point reduction or greater for symptom domains or items between baseline and 9 week assessments.

End point values	Standard Chemotherapy (Arm A)	Standard Chemotherapy + bevacizumab (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	159		
Units: percentage				
number (not applicable)	23	23		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events have to be reported from inclusion to 30 day following the end of administration of study treatments.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Safety Population : Arm A

Reporting group description:

The safety population will be defined as all patients who received at least one dose of treatment.

Reporting group title	Safety Population : Arm B

Reporting group description: -

Serious adverse events	Safety Population : Arm A	Safety Population : Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 224 (34.82%)	94 / 222 (42.34%)	
number of deaths (all causes)	178	164	
number of deaths resulting from adverse events	16	14	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Extradural neoplasm			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	3 / 224 (1.34%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 224 (0.00%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 224 (0.45%)	10 / 222 (4.50%)	
occurrences causally related to treatment / all	0 / 1	17 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 224 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 224 (0.45%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 224 (0.89%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
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	8 / 224 (3.57%)	6 / 222 (2.70%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 224 (0.89%)	5 / 222 (2.25%)	
occurrences causally related to treatment / all	2 / 3	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 224 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	15 / 224 (6.70%)	11 / 222 (4.95%)	
occurrences causally related to treatment / all	6 / 15	5 / 12	
deaths causally related to treatment / all	0 / 6	0 / 5	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	2 / 224 (0.89%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchial obstruction			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	5 / 224 (2.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 224 (0.89%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	3 / 224 (1.34%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 224 (0.89%)	8 / 222 (3.60%)	
occurrences causally related to treatment / all	1 / 2	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory distress			

subjects affected / exposed	1 / 224 (0.45%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory failure			
subjects affected / exposed	1 / 224 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 224 (0.89%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	10 / 224 (4.46%)	6 / 222 (2.70%)	
occurrences causally related to treatment / all	11 / 11	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	6 / 224 (2.68%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	6 / 6	5 / 5	
deaths causally related to treatment / all	1 / 1	0 / 0	
Platelet count decreased			
subjects affected / exposed	9 / 224 (4.02%)	6 / 222 (2.70%)	
occurrences causally related to treatment / all	10 / 10	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Expired product administered			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic haematoma			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 224 (0.45%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Extrasystoles			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infractio			

subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	0 / 224 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Headache			
subjects affected / exposed	0 / 224 (0.00%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	2 / 224 (0.89%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 224 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	7 / 224 (3.13%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	7 / 7	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	1 / 224 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 224 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 224 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 224 (1.34%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 224 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 224 (1.79%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	5 / 224 (2.23%)	7 / 222 (3.15%)	
occurrences causally related to treatment / all	5 / 6	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	2 / 224 (0.89%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subileus			
subjects affected / exposed	1 / 224 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 224 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			

subjects affected / exposed	0 / 224 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 224 (0.45%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercreatininaemia			
subjects affected / exposed	0 / 224 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 224 (0.45%)	5 / 222 (2.25%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fracture			
subjects affected / exposed	0 / 224 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	3 / 224 (1.34%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
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	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate infection			

subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 224 (1.34%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	1 / 2	0 / 0	
Septic shock			
subjects affected / exposed	0 / 224 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Staphylococcal sepsis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 224 (1.34%)	5 / 222 (2.25%)	
occurrences causally related to treatment / all	5 / 6	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 224 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety Population : Arm A	Safety Population : Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	224 / 224 (100.00%)	222 / 222 (100.00%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	22 / 224 (9.82%)	89 / 222 (40.09%)	
occurrences (all)	32	216	
Hypertension			
subjects affected / exposed	35 / 224 (15.63%)	134 / 222 (60.36%)	
occurrences (all)	106	477	
Thrombosis			
subjects affected / exposed	14 / 224 (6.25%)	10 / 222 (4.50%)	
occurrences (all)	34	19	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	173 / 224 (77.23%)	164 / 222 (73.87%)	
occurrences (all)	594	675	
Edema limbs			
subjects affected / exposed	25 / 224 (11.16%)	30 / 222 (13.51%)	
occurrences (all)	43	48	
Fever			
subjects affected / exposed	39 / 224 (17.41%)	25 / 222 (11.26%)	
occurrences (all)	55	33	
Reduced general condition			

subjects affected / exposed	21 / 224 (9.38%)	12 / 222 (5.41%)	
occurrences (all)	28	17	
Chest pain			
subjects affected / exposed	144 / 224 (64.29%)	136 / 222 (61.26%)	
occurrences (all)	491	441	
Pain			
subjects affected / exposed	22 / 224 (9.82%)	17 / 222 (7.66%)	
occurrences (all)	43	37	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	151 / 224 (67.41%)	143 / 222 (64.41%)	
occurrences (all)	488	483	
Cough			
subjects affected / exposed	83 / 224 (37.05%)	69 / 222 (31.08%)	
occurrences (all)	191	174	
Dysphonia			
subjects affected / exposed	5 / 224 (2.23%)	12 / 222 (5.41%)	
occurrences (all)	7	16	
Pulmonary embolism			
subjects affected / exposed	3 / 224 (1.34%)	11 / 222 (4.95%)	
occurrences (all)	6	17	
Rhinorrhea			
subjects affected / exposed	19 / 224 (8.48%)	10 / 222 (4.50%)	
occurrences (all)	28	25	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 224 (6.70%)	20 / 222 (9.01%)	
occurrences (all)	34	48	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 224 (3.57%)	11 / 222 (4.95%)	
occurrences (all)	27	37	
Hemoglobin decreased			
subjects affected / exposed	192 / 224 (85.71%)	165 / 222 (74.32%)	
occurrences (all)	1043	827	
Neutrophil count decreased			

subjects affected / exposed	179 / 224 (79.91%)	173 / 222 (77.93%)	
occurrences (all)	597	605	
Platelet count decreased			
subjects affected / exposed	122 / 224 (54.46%)	132 / 222 (59.46%)	
occurrences (all)	344	440	
Weight loss			
subjects affected / exposed	34 / 224 (15.18%)	38 / 222 (17.12%)	
occurrences (all)	79	103	
Creatinine increased			
subjects affected / exposed	16 / 224 (7.14%)	33 / 222 (14.86%)	
occurrences (all)	78	131	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 224 (7.59%)	50 / 222 (22.52%)	
occurrences (all)	22	119	
Paresthesia			
subjects affected / exposed	37 / 224 (16.52%)	22 / 222 (9.91%)	
occurrences (all)	77	56	
Dysgeusia			
subjects affected / exposed	24 / 224 (10.71%)	12 / 222 (5.41%)	
occurrences (all)	34	13	
Neuropathy			
subjects affected / exposed	23 / 224 (10.27%)	25 / 222 (11.26%)	
occurrences (all)	53	50	
Paresthesia of limbs			
subjects affected / exposed	14 / 224 (6.25%)	13 / 222 (5.86%)	
occurrences (all)	31	26	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	24 / 224 (10.71%)	15 / 222 (6.76%)	
occurrences (all)	69	24	
Vertigo			
subjects affected / exposed	13 / 224 (5.80%)	10 / 222 (4.50%)	
occurrences (all)	18	12	
Eye disorders			

Eyes tearing			
subjects affected / exposed	13 / 224 (5.80%)	13 / 222 (5.86%)	
occurrences (all)	22	26	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	16 / 224 (7.14%)	19 / 222 (8.56%)	
occurrences (all)	25	24	
Constipation			
subjects affected / exposed	70 / 224 (31.25%)	70 / 222 (31.53%)	
occurrences (all)	131	146	
Diarrhea			
subjects affected / exposed	34 / 224 (15.18%)	44 / 222 (19.82%)	
occurrences (all)	50	81	
Gastralgia			
subjects affected / exposed	20 / 224 (8.93%)	23 / 222 (10.36%)	
occurrences (all)	38	35	
Gastrooesophageal reflux			
subjects affected / exposed	8 / 224 (3.57%)	12 / 222 (5.41%)	
occurrences (all)	10	21	
Nausea			
subjects affected / exposed	166 / 224 (74.11%)	168 / 222 (75.68%)	
occurrences (all)	484	550	
Oral mucosal irritation			
subjects affected / exposed	33 / 224 (14.73%)	31 / 222 (13.96%)	
occurrences (all)	50	54	
Stomatitis			
subjects affected / exposed	10 / 224 (4.46%)	16 / 222 (7.21%)	
occurrences (all)	17	23	
Vomiting			
subjects affected / exposed	84 / 224 (37.50%)	89 / 222 (40.09%)	
occurrences (all)	172	162	
Gingival bleeding			
subjects affected / exposed	0 / 224 (0.00%)	13 / 222 (5.86%)	
occurrences (all)	0	31	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	34 / 224 (15.18%)	29 / 222 (13.06%)	
occurrences (all)	71	68	
Erythema			
subjects affected / exposed	24 / 224 (10.71%)	17 / 222 (7.66%)	
occurrences (all)	33	24	
Skin eruption			
subjects affected / exposed	11 / 224 (4.91%)	16 / 222 (7.21%)	
occurrences (all)	12	26	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 224 (0.89%)	37 / 222 (16.67%)	
occurrences (all)	5	162	
Renal failure			
subjects affected / exposed	10 / 224 (4.46%)	15 / 222 (6.76%)	
occurrences (all)	28	33	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	20 / 224 (8.93%)	17 / 222 (7.66%)	
occurrences (all)	29	30	
Joint pain			
subjects affected / exposed	12 / 224 (5.36%)	25 / 222 (11.26%)	
occurrences (all)	16	53	
Myalgia			
subjects affected / exposed	8 / 224 (3.57%)	12 / 222 (5.41%)	
occurrences (all)	8	14	
Pain neck/shoulder			
subjects affected / exposed	12 / 224 (5.36%)	16 / 222 (7.21%)	
occurrences (all)	26	29	
Rib pain			
subjects affected / exposed	7 / 224 (3.13%)	12 / 222 (5.41%)	
occurrences (all)	15	29	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	18 / 224 (8.04%)	19 / 222 (8.56%)	
occurrences (all)	38	39	

Oral candida			
subjects affected / exposed	16 / 224 (7.14%)	5 / 222 (2.25%)	
occurrences (all)	21	8	
Rhinitis			
subjects affected / exposed	7 / 224 (3.13%)	17 / 222 (7.66%)	
occurrences (all)	13	25	
Bronchitis			
subjects affected / exposed	20 / 224 (8.93%)	30 / 222 (13.51%)	
occurrences (all)	23	40	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	87 / 224 (38.84%)	88 / 222 (39.64%)	
occurrences (all)	189	181	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2007	A first modification of the protocol was done in October 2007 in order to add maintenance by bevacizumab.
15 December 2007	A 2nd modification was done in December 2007 in order to add new sites.
15 April 2008	A 3th modification was done in April 2008 in order to add new sites.
15 July 2008	A 4th modification was done in July 2008 in order to add new sites.
15 January 2009	A 5th modification was done in January 2009 in order to modify the timing of the protocol and to add new sites.
15 November 2009	A 6th modification was done in November 2009 in order to modify the number of patients.
15 June 2010	A 7th amendment was made in June 2010 to modify the sponsor and the merger of the consent.
15 April 2011	An 8th amendment was made in April 2011 to relax the inclusion criteria on cancer history and to add new sites.
15 November 2011	A 9th modification was done in November 2011 in order to add new sites.
15 March 2012	A 10th modification was done in March 2012 in order to : add new sites, clarify what to do in case of venous thrombosis and high blood pressure and update of the bevacizumab IB, extend the duration of treatment interruption during the maintenance phase.
15 October 2014	A 11th modification was done in October 2014 in order to modify the PI for 3 sites and to extend the duration of the study.
15 September 2015	A 12th modification was done in September 2015 in order to add a second interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Open-label trial. Assessment of QoL could have been slightly altered by the absence of masking.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26719230