Clinical trial results:
phase II study evaluating the interest of the re-introduction of pemetrexed and platinum (cisplatin or carboplatin) with prolonged angiogenic blocking by bevacizumab in non squamous non small cell lung cancer of advanced stage.

Summary

EudraCT number	2012-002647-18
Trial protocol	FR
Global end of trial date	13 October 2017
Results information	
Result version number	v1 (current)
This version publication date	13 March 2022
First version publication date	13 March 2022

Trial information

Trial identification	
Sponsor protocol code	IFCT-1102
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01705184
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	Clinical trial informations, IFCT, 33 15681045, contact@ifct.fr
Scientific contact	Clinical trial informations, IFCT, 33 15681045, 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	31 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Feasibility of cisplatin re-introduction (stop-and-go strategy) in patients with advanced nonsquamous non-small cell lung cancer

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	83
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From December 2012 to August 2014, 14 hospital centres from the French Cooperative Thoracic Intergroup included 120 patients.

Pre-assignment

Screening details:

Adult patients with previously untreated documented advanced nsqNSCLC were eligible to if they presented with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumours (RECIST V.1.1). Patients had to be in good health condition (Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤1.

Period 1

Period 1 title	Sequence 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	cisplatin + pemetrexed + bevacizumab

Arm description: -

Arm type	Single ARM study
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 mg/m² every 3 weeks for 3 cycles

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

Dosage and administration details:

500 mg/m² every 3 weeks for 3 cycles

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

Dosage and administration details:

AUC 5 every 3 weeks
Cisplatin could be switched to carboplatin according to investigator decision in case of unacceptable cisplatin toxicity.

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

Dosage and administration details:
7,5 mg/kg every 3 weeks until progression or toxicity

Number of subjects in period 1	cisplatin + pemetrexed + bevacizumab
Started	120
Completed	68
Not completed	52
Adverse event, serious fatal	1
Patient's choice	1
Treatment not started	2
Physician decision	9
Adverse event, non-fatal	12
Intercurrent disease	4
Related to cancer	3
Treatment completed but sequence 2 not started	2
Lack of efficacy	13
Protocol deviation	5

Period 2

Period 2 title	Sequence 2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	cisplatin + pemetrexed + bevacizumab

Arm description: -

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

Dosage and administration details:
75 mg/m² every 3 weeks for 3 cycles

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

Dosage and administration details:

500 mg/m² every 3 weeks until progression or toxicity

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

Dosage and administration details:

AUC 5 every 3 weeks
Cisplatin could be switched to carboplatin according to investigator decision in case of unacceptable cisplatin toxicity.

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

Dosage and administration details:

7,5 mg/kg every 3 weeks until progression or toxicity

Number of subjects in period 2	cisplatin + pemetrexed + bevacizumab
Started	68
Completed	37
Not completed	31
withdrawal form sequence 2	28
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	Sequence 1

Reporting group description: -

Reporting group values	Sequence 1	Total	
Number of subjects	120	120	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	60.19		
standard deviation	± 8.54	-	
Gender categorical Units: Subjects			
Female	43	43	
Male	77	77	
Smoking status Units: Subjects			
Never smoker	21	21	
former/current smoker	99	99	
ECOG performance status Units: Subjects			
PS = 0	60	60	
PS = 1	60	60	
Disease stage at inclusion Units: Subjects			
M0	1	1	
M1a	39	39	
M1b	80	80	
Pathological type Units: Subjects			
Adenocarcinoma without bronchioloalveolar componen	113	113	
Adenocarcinoma with bronchioloalveolar component	2	2	
Large cell carcinoma	5	5	

No of pack-years			
Units: Pack-years			
median	40.0		
full range (min-max)	5.0 to 160.0	-	

End points

End points reporting groups

Reporting group title	cisplatin + pemetrexed + bevacizumab
Reporting group description: -	
Reporting group title	cisplatin + pemetrexed + bevacizumab
Reporting group description: -	
Subject analysis set title	Efficacy population sequence 1
Subject analysis set type	Per protocol
Subject analysis set description: Patients without major deviation to inclusion or exclusion criteria	
Subject analysis set title	Safety population sequence 1
Subject analysis set type	Safety analysis
Subject analysis set description: Patients who received at least one treatment	
Subject analysis set title	Efficacy population sequence 2
Subject analysis set type	Per protocol
Subject analysis set description: Patients without major deviation to inclusion or exclusion criteria	
Subject analysis set title	ITT population sequence 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: All registered	
Subject analysis set title	Safety population for sequence 2
Subject analysis set type	Safety analysis
Subject analysis set description: Patients who received at least one treatment	

Primary: Proportion of patients who received three cycles of chemotherapy without dose reduction of platinum-based chemotherapy during sequence 2

End point title	Proportion of patients who received three cycles of chemotherapy without dose reduction of platinum-based chemotherapy during sequence 2[1]
End point description:	
End point type	Primary
End point timeframe: 9 weeks after starting sequence 2	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Single arm study

End point values	Efficacy population sequence 2			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: percent				
number (confidence interval 95%)	56.9 (45.1 to 73.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS sequence 1

End point title	PFS sequence 1

End point description:

time from inclusion to the first disease progression or death

End point type	Secondary

End point timeframe:

Up to 25 months

End point values	cisplatin + pemetrexed + bevacizumab	Efficacy population sequence 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	113[2]	113		
Units: month				
median (confidence interval 95%)	5.6 (5.0 to 6.3)	5.6 (5.0 to 6.3)		

Notes:

[2] - Per protocol population

Statistical analyses

No statistical analyses for this end point

Secondary: PFS sequence 2

End point title	PFS sequence 2

End point description:

time from first to second disease progression or death

End point type	Secondary

End point timeframe:

Up to 25 months

End point values	Efficacy population sequence 2			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: month				
median (confidence interval 95%)	6.8 (5.8 to 8.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control duration

End point title	Disease control duration
End point description: PFS sequence 1 + PFS sequence 2	
End point type	Secondary
End point timeframe: Up to 24 months	

End point values	Efficacy population sequence 2			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: month				
median (confidence interval 95%)	12.4 (11.2 to 14.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate after sequence 2

End point title	Disease control rate after sequence 2
End point description:	
End point type	Secondary
End point timeframe: Up to 24 months	

End point values	Efficacy population sequence 2			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: percent				
number (confidence interval 95%)	75.4 (64.9 to 85.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease response rate after sequence 2

End point title	Disease response rate after sequence 2

End point description:

End point type	Secondary

End point timeframe:

Up to 24 months

End point values	Efficacy population sequence 2			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: percent				
number (confidence interval 95%)	15.4 (6.6 to 24.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Up to 24 months

End point values	Efficacy population sequence 1			
Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: month				
median (confidence interval 95%)	17.7 (13.1 to 21.6)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall survival from sequence 2

End point title	Overall survival from sequence 2

End point description:

End point type	Post-hoc

End point timeframe:

Up to 24 months

End point values	Efficacy population sequence 2			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: month				
median (confidence interval 95%)	20.5 (16.9 to 26.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent signature until 30 days after the last received treatment

Adverse event reporting additional description:

The maximal grade of adverse events was collected by cycle of treatment.
Occurence of non-serious adverse events non available in the statistical report.
Only non-serious adverse events related to study treatment are available in the statistical report.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Safety population sequence 1
Reporting group description: -	
Reporting group title	Safety population sequence 2

Reporting group description: -

Serious adverse events	Safety population sequence 1	Safety population sequence 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 118 (30.51%)	24 / 68 (35.29%)	
number of deaths (all causes)	40	35	
number of deaths resulting from adverse events	10	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial carcinoma			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Coronary artery stenosis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	0 / 118 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 118 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 118 (1.69%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 118 (0.85%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	7 / 118 (5.93%)	9 / 68 (13.24%)	
occurrences causally related to treatment / all	5 / 9	14 / 20	
deaths causally related to treatment / all	0 / 2	0 / 3	
Malaise			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	2 / 118 (1.69%)	0 / 68 (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			
Haemoptysis			
subjects affected / exposed	1 / 118 (0.85%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Lung disorder			
subjects affected / exposed	2 / 118 (1.69%)	3 / 68 (4.41%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 118 (0.85%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	3 / 118 (2.54%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 118 (0.85%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 118 (0.00%)	1 / 68 (1.47%)	
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			
Bone marrow failure			
subjects affected / exposed	4 / 118 (3.39%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 118 (0.85%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 118 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 118 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 118 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorder			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 118 (1.69%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (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	2 / 118 (1.69%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 118 (2.54%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 118 (0.85%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 118 (1.69%)	3 / 68 (4.41%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dysphagia			
subjects affected / exposed	0 / 118 (0.00%)	4 / 68 (5.88%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 118 (2.54%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	0 / 118 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 118 (0.00%)	1 / 68 (1.47%)	
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			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (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 / 118 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related infection			
subjects affected / exposed	1 / 118 (0.85%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	3 / 118 (2.54%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Infection			
subjects affected / exposed	0 / 118 (0.00%)	3 / 68 (4.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 118 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	5 / 118 (4.24%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	3 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
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 sequence 1	Safety population sequence 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 118 (100.00%)	66 / 68 (97.06%)	
Vascular disorders			
Epistaxis			

subjects affected / exposed	39 / 118 (33.05%)	22 / 68 (32.35%)	
occurrences (all)	39	22	
Hypertension			
subjects affected / exposed	38 / 118 (32.20%)	16 / 68 (23.53%)	
occurrences (all)	38	16	
Haemoptysis			
subjects affected / exposed	6 / 118 (5.08%)	4 / 68 (5.88%)	
occurrences (all)	6	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	74 / 118 (62.71%)	48 / 68 (70.59%)	
occurrences (all)	74	48	
Fatigue			
subjects affected / exposed	7 / 118 (5.93%)	4 / 68 (5.88%)	
occurrences (all)	7	4	
General physical health deterioration			
subjects affected / exposed	5 / 118 (4.24%)	9 / 68 (13.24%)	
occurrences (all)	5	9	
Oedema peripheral			
subjects affected / exposed	4 / 118 (3.39%)	6 / 68 (8.82%)	
occurrences (all)	4	6	
Pyrexia			
subjects affected / exposed	2 / 118 (1.69%)	5 / 68 (7.35%)	
occurrences (all)	2	5	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	7 / 118 (5.93%)	4 / 68 (5.88%)	
occurrences (all)	7	4	
Rhinorrhoea			
subjects affected / exposed	2 / 118 (1.69%)	6 / 68 (8.82%)	
occurrences (all)	2	6	
Dyspnoea			
subjects affected / exposed	1 / 118 (0.85%)	4 / 68 (5.88%)	
occurrences (all)	1	4	
Investigations			

Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 118 (7.63%)	10 / 68 (14.71%)	
occurrences (all)	9	10	
Weight decreased			
subjects affected / exposed	8 / 118 (6.78%)	3 / 68 (4.41%)	
occurrences (all)	8	3	
Alanine aminotransferase increased			
subjects affected / exposed	7 / 118 (5.93%)	8 / 68 (11.76%)	
occurrences (all)	7	8	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 118 (3.39%)	7 / 68 (10.29%)	
occurrences (all)	4	7	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 118 (1.69%)	6 / 68 (8.82%)	
occurrences (all)	2	6	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	11 / 118 (9.32%)	3 / 68 (4.41%)	
occurrences (all)	11	3	
Paraesthesia			
subjects affected / exposed	11 / 118 (9.32%)	7 / 68 (10.29%)	
occurrences (all)	11	7	
Headache			
subjects affected / exposed	9 / 118 (7.63%)	6 / 68 (8.82%)	
occurrences (all)	9	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	62 / 118 (52.54%)	46 / 68 (67.65%)	
occurrences (all)	62	46	
Neutropenia			
subjects affected / exposed	56 / 118 (47.46%)	31 / 68 (45.59%)	
occurrences (all)	56	31	
Thrombocytopenia			
subjects affected / exposed	30 / 118 (25.42%)	21 / 68 (30.88%)	
occurrences (all)	30	21	
Febrile neutropenia			

subjects affected / exposed	1 / 118 (0.85%)	4 / 68 (5.88%)	
occurrences (all)	1	4	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	7 / 118 (5.93%)	3 / 68 (4.41%)	
occurrences (all)	7	3	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	8 / 118 (6.78%)	11 / 68 (16.18%)	
occurrences (all)	8	11	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	64 / 118 (54.24%)	38 / 68 (55.88%)	
occurrences (all)	64	35	
Stomatitis			
subjects affected / exposed	26 / 118 (22.03%)	13 / 68 (19.12%)	
occurrences (all)	26	13	
Vomiting			
subjects affected / exposed	24 / 118 (20.34%)	14 / 68 (20.59%)	
occurrences (all)	24	14	
Constipation			
subjects affected / exposed	15 / 118 (12.71%)	12 / 68 (17.65%)	
occurrences (all)	15	12	
Diarrhoea			
subjects affected / exposed	14 / 118 (11.86%)	13 / 68 (19.12%)	
occurrences (all)	14	13	
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 118 (6.78%)	1 / 68 (1.47%)	
occurrences (all)	8	1	
Dysphagia			
subjects affected / exposed	2 / 118 (1.69%)	4 / 68 (5.88%)	
occurrences (all)	2	4	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 118 (6.78%)	4 / 68 (5.88%)	
occurrences (all)	8	4	
Renal and urinary disorders			

Proteinuria			
subjects affected / exposed	17 / 118 (14.41%)	12 / 68 (17.65%)	
occurrences (all)	17	12	
Renal failure			
subjects affected / exposed	1 / 118 (0.85%)	6 / 68 (8.82%)	
occurrences (all)	1	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 118 (5.93%)	1 / 68 (1.47%)	
occurrences (all)	7	1	
Myalgia			
subjects affected / exposed	6 / 118 (5.08%)	1 / 68 (1.47%)	
occurrences (all)	6	1	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	15 / 118 (12.71%)	7 / 68 (10.29%)	
occurrences (all)	15	7	
Oral candidiasis			
subjects affected / exposed	2 / 118 (1.69%)	4 / 68 (5.88%)	
occurrences (all)	2	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 118 (19.49%)	22 / 68 (32.35%)	
occurrences (all)	23	22	
Hypercreatinaemia			
subjects affected / exposed	18 / 118 (15.25%)	28 / 68 (41.18%)	
occurrences (all)	18	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2013	Clarification of inclusion criteria (only patient with metastatic disease are eligible). Correction of the timing of blood sample for ancillary study
09 September 2014	Increased in patients number

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/30094074