Clinical trial results:
Randomized Phase II-III Study Comparing Bevacizumab 7.5 mg/kg in Combination with Chemotherapy Versus Chemotherapy in Extensive-Disease Small-Cell Lung Cancer After Response to PCDE or PE Chemotherapy
PCDE: cisPlatin – Cyclophosphamide – epiDoxorubicin – Etoposide
PE: cisPlatin – Etoposide

Summary

EudraCT number	2009-010187-42
Trial protocol	FR
Global end of trial date	26 July 2013

Results information

Result version number	v1 (current)
This version publication date	08 January 2017
First version publication date	08 January 2017

Trial information

Trial identification

Sponsor protocol code	IFCT-0802

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00930891
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IFCT
Sponsor organisation address	10 rue de la Grange-Batelière, PARIS, France,
Public contact	Sponsor, IFCT, contact@ifct.fr
Scientific contact	Sponsor, IFCT, 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	26 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2013
Global end of trial reached?	Yes
Global end of trial date	26 July 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Objective response rate (complete response + partial response) after 4 cycles.

Protection of trial subjects:

Reductions of dose of the study treatment.
Best supportive care treatment

Background therapy:

Chemotherapy is thus the standard first-line treatment for small-cell lung cancer and is the only anticancer treatment with demonstrated beneficial effect for patients with extensive-stage disease [Chute, 1999]. Cisplatin-etoposide combination chemotherapy is active in first-line therapy and is the reference combination for many collaborative groups [Chute et al, 1999; Maksymiuk et al, 1994; Ihde et al, 1994]. Two meta-analyses of literature data showed that, as for the combination chemotherapy, chemotherapies based on either one of these two drugs prolong the lives of patients [Pujol et al, 2000; Paesmans et al, 2000]. Furthermore, a recent in vitro study suggests that they have distinct synergistic effects [Jensen et al, 1997]. However, the proportion of patients surviving beyond two years remains below 10%; the low two-year survival rate is due to chemotherapy-resistant relapse [Hansen and Kristjansen, 1991; Aisner J, 1996]. An explanation for this could be the selection of a chemotherapy-resistant phenotype of tumor cells to the induction treatment. New chemotherapy methods are currently being studied to avoid or circumvent this chemotherapy-resistant relapse.

Evidence for comparator: -

Actual start date of recruitment	22 September 2009
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: 147
Worldwide total number of subjects	147
EEA total number of subjects	147

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	111
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period : 22/09/2009 to 19/10/2011.
Territory : France

Pre-assignment

Screening details:

previously untreated extensive small-cell lung cancer

Period 1

Period 1 title	Inclusion period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Chemotherapy

Arm description:

All patient included received 2 cycles of chemotherapy (PE or PCDE)

Arm type	Same treatment for all patients
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 mg/m², Day 2 every 21 days for patient receiving PCDE treatment
80 mg/m², Day 2 every 21 days for patient receiving PE treatment

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

Dosage and administration details:

75 mg/m² Day 1, Day 2 and Day 3, every 21 days for patient receiving PCDE treatment
120 mg/m² Day 1, Day 2 and Day 3, every 21 days for patient receiving PE treatment

Investigational medicinal product name	4'-epidoxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/m², Day 1 every 21 days for patient receiving PCDE treatment only

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

Dosage and administration details:

300 mg/m², Day 1, Day 2, Day 3 every 21 days for patient receiving PCDE treatment only

Number of subjects in period 1	Chemotherapy
Started	147
Completed	138
Not completed	9
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Protocol deviation	1
Lack of efficacy	6

Period 2	
Period 2 title	Randomization period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Chemotherapy alone
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/m², Day 2 every 21 days for patient receiving PCDE treatment 80 mg/m², Day 2 every 21 days for patient receiving PE treatment	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/m² Day 1, Day 2 and Day 3, every 21 days for patient receiving PCDE treatment 120 mg/m² Day 1, Day 2 and Day 3, every 21 days for patient receiving PE treatment	
Investigational medicinal product name	4'-epidoxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: 30 mg/m², Day 1 every 21 days for patient receiving PCDE treatment only	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 300 mg/m², Day 1, Day 2, Day 3 every 21 days for patient receiving PCDE treatment only	
Arm title	Chemotherapy + bevacizumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/m², Day 2 every 21 days for patient receiving PCDE treatment 80 mg/m², Day 2 every 21 days for patient receiving PE treatment	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/m² Day 1, Day 2 and Day 3, every 21 days for patient receiving PCDE treatment 120 mg/m² Day 1, Day 2 and Day 3, every 21 days for patient receiving PE treatment	
Investigational medicinal product name	4'-epidoxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 30 mg/m², Day 1 every 21 days for patient receiving PCDE only	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 300 mg/m², Day 1, Day 2, Day 3 every 21 days for patient receiving PCDE only	
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 7,5 mg/m² Day 1 every 21 days	

Number of subjects in period 2[1]	Chemotherapy alone	Chemotherapy + bevacizumab
Started	37	37
Completed	31	35
Not completed	6	2
Adverse event, non-fatal	4	-
Lack of efficacy	2	1
Protocol deviation	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 64 subjects excluded because they not fulfill the randomization criteria

Baseline characteristics

Reporting groups	
Reporting group title	Inclusion period

Reporting group description: -

Reporting group values	Inclusion period	Total	
Number of subjects	147	147	
Age categorical Units: Subjects			
Adults (18-64 years)	111	111	
From 65-84 years	36	36	
Gender categorical Units: Subjects			
Female	39	39	
Male	108	108	
Produits de chimiothérapie Units: Subjects			
PCDE	20	20	
PE	127	127	
Performance status Units: Subjects			
PS 0 - 1	118	118	
PS 2	29	29	

End points

End points reporting groups	
Reporting group title	Chemotherapy
Reporting group description:	
All patient included received 2 cycles of chemotherapy (PE or PCDE)	
Reporting group title	Chemotherapy alone
Reporting group description: -	
Reporting group title	Chemotherapy + bevacizumab
Reporting group description: -	

Primary: Objective reponse rate	
End point title	Objective reponse rate
End point description:	
End point type	Primary
End point timeframe:	
4 cycles after andomization	

End point values	Chemotherapy alone	Chemotherapy + bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	37		
Units: Number of patient				
Complete response	0	0		
Partial response	34	34		
Stable disease	0	0		
Progression	1	1		
Not done	1	0		
Non evaluable	1	2		

Statistical analyses

Statistical analysis title	Objective reponse rate
Comparison groups	Chemotherapy alone v Chemotherapy + bevacizumab
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Objective Reponse rate

End point title	Objective Reponse rate

End point description:

End point type	Secondary

End point timeframe:
after 6 cycles

End point values	Chemotherapy alone	Chemotherapy + bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	37		
Units: Number of patient				
Complete response	3	1		
Partial Response	23	27		
Stable disease	0	2		
Progression disease	4	3		
Evaluation not done	2	0		
Non evaluable	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:
Time between randomization and progression or death of any cause

End point values	Chemotherapy alone	Chemotherapy + bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	37		
Units: Months				
median (confidence interval 95%)	5.5 (4.9 to 6)	5.3 (5 to 6.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survivall

End point title	Overall survivall

End point description:

End point type	Secondary

End point timeframe:

Time between randomization and death any cause.

End point values	Chemotherapy alone	Chemotherapy + bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	37		
Units: Months				
median (confidence interval 95%)	13 (9.7 to 19.8)	11.1 (8.6 to 13.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Between inclusion and 30 days after the last injection of study drugs	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Chemotherapy
Reporting group description:	
All patient included received 2 cycles of chemotherapy (PE or PCDE)	
Reporting group title	Chemotherapy alone
Reporting group description:	
Patients randomized in the arm chemotherapy alone	
Reporting group title	Chemotherapy + bevacizumab
Reporting group description:	
Patients randomized in the arm chemotherapy + bevacizumab	

Serious adverse events	Chemotherapy	Chemotherapy alone	Chemotherapy + bevacizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 147 (33.33%)	6 / 37 (16.22%)	13 / 37 (35.14%)
number of deaths (all causes)	140	37	36
number of deaths resulting from adverse events	4	0	1
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 147 (2.04%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	3 / 37 (8.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis superficial			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute pulmonary oedema			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	2 / 147 (1.36%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiac disorder			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 147 (0.00%)	1 / 37 (2.70%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intracranial hemorrhage			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Personality change			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Seizure			

subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Aphasia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Consciousness disturb			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial hypertension			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			

subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reduced General Condition			
subjects affected / exposed	3 / 147 (2.04%)	0 / 37 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sleep disorder			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile aplasia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemoglobin decreased			

subjects affected / exposed	2 / 147 (1.36%)	1 / 37 (2.70%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	3 / 147 (2.04%)	3 / 37 (8.11%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	2 / 147 (1.36%)	2 / 37 (5.41%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	2 / 2	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 37 (2.70%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 147 (1.36%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 147 (2.04%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	6 / 147 (4.08%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorexia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hemoptysis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumopathy			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Progression of bronchial progression			
subjects affected / exposed	3 / 147 (2.04%)	0 / 37 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Hepatobiliary disorders			

Hepatic cytolysis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Acute Renal failure			
subjects affected / exposed	3 / 147 (2.04%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 147 (0.68%)	1 / 37 (2.70%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abcess			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	4 / 147 (2.72%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	5 / 147 (3.40%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	4 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	2 / 147 (1.36%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Chemotherapy	Chemotherapy alone	Chemotherapy + bevacizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	146 / 147 (99.32%)	37 / 37 (100.00%)	35 / 37 (94.59%)
Vascular disorders			
Venous thromboembolism disorder			
subjects affected / exposed	5 / 147 (3.40%)	6 / 37 (16.22%)	5 / 37 (13.51%)
occurrences (all)	7	13	14
General disorders and administration site conditions			
Generals disorders			
subjects affected / exposed	75 / 147 (51.02%)	30 / 37 (81.08%)	29 / 37 (78.38%)
occurrences (all)	228	131	172
Haemorrhage			
subjects affected / exposed	3 / 147 (2.04%)	2 / 37 (5.41%)	7 / 37 (18.92%)
occurrences (all)	5	3	17
Pain			
subjects affected / exposed	49 / 147 (33.33%)	14 / 37 (37.84%)	24 / 37 (64.86%)
occurrences (all)	173	58	69
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	63 / 147 (42.86%)	14 / 37 (37.84%)	16 / 37 (43.24%)
occurrences (all)	351	77	75
Cardiac disorders			
Cardiac Disorders			
subjects affected / exposed	6 / 147 (4.08%)	3 / 37 (8.11%)	1 / 37 (2.70%)
occurrences (all)	20	21	62
Hypertension			
subjects affected / exposed	6 / 147 (4.08%)	2 / 37 (5.41%)	7 / 37 (18.92%)
occurrences (all)	10	13	60

Nervous system disorders			
Neurological disorder			
subjects affected / exposed	19 / 147 (12.93%)	9 / 37 (24.32%)	13 / 37 (35.14%)
occurrences (all)	90	26	51
Peripheral neurological disorder			
subjects affected / exposed	6 / 147 (4.08%)	12 / 37 (32.43%)	12 / 37 (32.43%)
occurrences (all)	11	19	23
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	94 / 147 (63.95%)	32 / 37 (86.49%)	34 / 37 (91.89%)
occurrences (all)	165	170	181
Neutrophil count decreased			
subjects affected / exposed	78 / 147 (53.06%)	17 / 37 (45.95%)	22 / 37 (59.46%)
occurrences (all)	141	74	99
Thrombocytopenia			
subjects affected / exposed	69 / 147 (46.94%)	25 / 37 (67.57%)	28 / 37 (75.68%)
occurrences (all)	114	103	130
Ear and labyrinth disorders			
Auditory disorder			
subjects affected / exposed	5 / 147 (3.40%)	3 / 37 (8.11%)	5 / 37 (13.51%)
occurrences (all)	13	13	20
Eye disorders			
Occular disorder			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	88 / 147 (59.86%)	23 / 37 (62.16%)	29 / 37 (78.38%)
occurrences (all)	305	152	180
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	43 / 147 (29.25%)	15 / 37 (40.54%)	12 / 37 (32.43%)
occurrences (all)	94	81	61
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 147 (0.00%)	0 / 37 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	4
Renal disorders			

subjects affected / exposed	12 / 147 (8.16%)	8 / 37 (21.62%)	9 / 37 (24.32%)
occurrences (all)	18	18	24
Cystitis and urinary retention			
subjects affected / exposed	1 / 147 (0.68%)	0 / 37 (0.00%)	6 / 37 (16.22%)
occurrences (all)	1	0	6
Musculoskeletal and connective tissue disorders			
Cramps			
subjects affected / exposed	5 / 147 (3.40%)	0 / 37 (0.00%)	0 / 37 (0.00%)
occurrences (all)	8	0	0
Infections and infestations			
Infection			
subjects affected / exposed	14 / 147 (9.52%)	4 / 37 (10.81%)	11 / 37 (29.73%)
occurrences (all)	41	13	44
Metabolism and nutrition disorders			
Metabolic disorder			
subjects affected / exposed	27 / 147 (18.37%)	12 / 37 (32.43%)	13 / 37 (35.14%)
occurrences (all)	148	100	125

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2009	- New investigators - Modification of exclusion criteria: patient with cerebral metastasis are eligible if the metastasis are asymptomatic
26 October 2009	- Modification of the sponsor adress - 4 new investigators - The exclusion criteria regarding the tumor invading large vessels or invading the proximal tracheobronchial tree is transfered in randomisation criteria
19 October 2011	- New investigators - Principal investigators modification for 3 sites - Insurance modification - IDMC only for the phase III part of the trial

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.

Occurence of adverse events not precisely recorded in the CRF.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25688059