Clinical trial results:
RANDOMIZED MULTICENTER PHASE III STUDY IN PATIENTS WITH LOCALLY ADVANCED ADENOCARCINOMA OF THE PANCREAS: GEMCITABINE WITH OR WITHOUT CHEMORADIOTHERAPY AND WITH OR WITHOUT ERLOTINIB

Summary

EudraCT number	2007-001174-81
Trial protocol	FR BE SE
Global end of trial date	31 January 2014

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	D07-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GERCOR
Sponsor organisation address	151 rue du faubourg saint Antoine, PARIS, France, 75011
Public contact	Regulatory affairs, GERCOR, 33 140298500, regulatory.affairs@gercor.com.fr
Scientific contact	Regulatory Affairs, GERCOR, 33 140298500, regulatory.affairs@gercor.com.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 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2014
Global end of trial reached?	Yes
Global end of trial date	31 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether administrating a chemoradiotherapy in patients whose tumor is controlled after 4 months of induction chemotherapy (CT) increases survival compared to continue the same CT.

Protection of trial subjects:

Before the chemotherapy protocol, the patient will receive the antiemetic which is generally used by the hospital in charge of the patient and a preventive anti-emetic treatment 1hour before each radiation session is recommended.
If necessary, anti-emetic or anti-diarrhoea treatment can be prescribed to treat symptoms. The systematic prescription of anti-gastric secretion medicine (anti-H2 or PPI) is highly recommended during radiation as well as six months afterwards to reduce gastric acid secretion and prevent the risk of upper gastrointestinal ulcer.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 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	Sweden: 17
Country: Number of subjects enrolled	Belgium: 46
Country: Number of subjects enrolled	France: 347
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	New Zealand: 5
Worldwide total number of subjects	442
EEA total number of subjects	410

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)	156
From 65 to 84 years	273
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Between Feb. 2008 and Dec.2011,a total of 449 patients from 80 centers in France, Australia, New Zealand, Belgium and Sweden were enrolled. Of these, 4 patients had missing data, 2 had a periampullary cancer, and 1 had a history of other previous malignancy that has been in complete remission for less than 5 years, thus leaving 442eligible patients

Pre-assignment

Screening details:

Eligible patients were at least 18 years of age; histologically or cytologically confirmed stage III locally advanced pancreatic cancer; a measurable or evaluable disease as assessed according to the RECIST1.0 criteria; Performance status 0-2; adequate biological, hematological and renal parameters; no prior chemotherapy or radiation therapy.

Period 1

Period 1 title	First randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	First randomization - Gemcitabine

Arm description: -

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

Dosage and administration details:

Gemcitabine: 1000mg/m² - 30 min infusion (Day 1, D8, D15, D22, D29, D36, D43 then after first evaluation D57, D64, D71, D85, D92 and D99)

Arm title	First randomization - Gemcitabine plus Erlotinib

Arm description: -

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

Dosage and administration details:

Gemcitabine: 1000mg/m² - 30 min infusion, (D1, D8, D15, D22, D29, D36, D43 then after firts evaluation D57, D64, D71, D85, D92, D99)

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib :100mg dose per day at least one hour before or two hours after meals, during 4 months.

Number of subjects in period 1	First randomization - Gemcitabine	First randomization - Gemcitabine plus Erlotinib
Started	223	219
Completed	223	219

Period 2	
Period 2 title	Second Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	second randomization - A1 - Gemcitabine
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: Gemcitabine 1000mg/m², 30 min infusion (on D113, D120, D127, D141, D148 and D155)	
Arm title	Second randomization - B1 - Gemcitabine plus Erlotinib
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: Gemcitabine :1000mg/m² - 30 min infusion (on D113, D120, D127, D141, D148 and D155)	
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Erlotinib: 100mg dose per day at least one hour before or two hours after meals during 2 months. After D155, erlotinib 150mg dose per day until progression	
Arm title	Second Randomization - A2 - Chemoradiotherapy

Arm description:	
radiation therapy 54Gy and concomitant capecitabine	
Arm type	Experimental
Investigational medicinal product name	capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Capecitabine per os at a total dose of 1600mg/m² (5 days per week). Then stop unitl progression	
Arm title	second Randomization - B2 - Chemoradiotherapy
Arm description:	
Radiation therapy 54Gy and concomitant capecitabine. Then reintroduction of erlotinib alone 150mg per day until progression.	
Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Capecitabine :per os at a total dose of 1600mg/m² (5 days per week).	
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Erlotinib : réintroduction after radiation therapy and concomitant capecitabine. Dose : 150mg per day until progression	

Number of subjects in period 2[1]	second randomization - A1 - Gemcitabine	Second randomization - B1 - Gemcitabine plus Erlotinib	Second Randomization - A2 - Chemoradiotherapy
Started	68	67	68
Completed	68	67	68

Number of subjects in period 2[1]	second Randomization - B2 - Chemoradiotherapy
Started	66
Completed	66

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: 173 patients were excluded before seconde randomization : death(9 patients);

Progressive disease (102 patients); Intercurrent disease (6 patients); Toxicity (15 patients); Delay of radiotherapy >7 days (1 patient); Delay of chemotherapy (10 patients); Investigator decision (16 patients); Patients' decision (11 patients); Other reason (3 patients)

Baseline characteristics

Reporting groups	
Reporting group title	First randomization - Gemcitabine
Reporting group description: -	
Reporting group title	First randomization - Gemcitabine plus Erlotinib
Reporting group description: -	

Reporting group values	First randomization - Gemcitabine	First randomization - Gemcitabine plus Erlotinib	Total
Number of subjects	223	219	442
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	81	75	156
From 65-84 years	138	135	273
85 years and over	4	9	13
Age continuous Units: years			
median	64	63	
inter-quartile range (Q1-Q3)	57 to 70	58 to 71	-
Gender categorical Units: Subjects			
Female	106	108	214
Male	117	111	228
WHO Performance status score Units: Subjects			
PS0	109	88	197
PS1	91	112	203
PS2	15	16	31
Unknown	8	3	11
Tumor location in the pancreas Units: Subjects			
Head	146	156	302
Body and tail	76	62	138
Unknown	1	1	2
Grading Units: Subjects			
Well differenciated	56	51	107
Moderately differentiated	37	38	75
Poorly differenciated	18	23	41
Grade cannot be assessed	40	43	83

Missing	72	64	136
Node status Units: Subjects			
N0	134	124	258
N1	85	94	179
Unknown	4	1	5
Vascular invasion Units: Subjects			
Superior mesenteric artery	80	64	144
Coeliac trunk	96	92	188
Hepatic trunk	10	15	25
No	34	45	79
Missing	3	3	6

Subject analysis sets	
Subject analysis set title	Second randomization - Chemotherapy
Subject analysis set type	Sub-group analysis
Subject analysis set description: ARM B1 - gemcitabine plus erlotinib	
Subject analysis set title	Second randomization - Chemoradiotherapy
Subject analysis set type	Sub-group analysis
Subject analysis set description: ARM B2 - radiation therapy 54Gy and concomitant capecitabine per os	

Reporting group values	Second randomization - Chemotherapy	Second randomization - Chemoradiotherapy	
Number of subjects	136	133	
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)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	63	62	
inter-quartile range (Q1-Q3)	57 to 70	55 to 70	
Gender categorical Units: Subjects			
Female	60	75	
Male	76	58	

WHO Performance status score Units: Subjects			
PS0	76	64	
PS1	48	60	
PS2	8	7	
Unknown	4	2	
Tumor location in the pancreas Units: Subjects			
Head	93	88	
Body and tail	43	44	
Unknown	0	1	
Grading Units: Subjects			
Well differenciated	33	31	
Moderately differentiated	23	22	
Poorly differenciated	10	9	
Grade cannot be assessed	25	28	
Missing	45	43	
Node status Units: Subjects			
N0	79	77	
N1	57	54	
Unknown	0	2	
Vascular invasion Units: Subjects			
Superior mesenteric artery	50	40	
Coeliac trunk	57	59	
Hepatic trunk	7	11	
No	20	23	
Missing	2	0	

End points

End points reporting groups

Reporting group title	First randomization - Gemcitabine
Reporting group description: -	
Reporting group title	First randomization - Gemcitabine plus Erlotinib
Reporting group description: -	
Reporting group title	second randomization - A1 - Gemcitabine
Reporting group description: -	
Reporting group title	Second randomization - B1 - Gemcitabine plus Erlotinib
Reporting group description: -	
Reporting group title	Second Randomization - A2 - Chemoradiotherapy
Reporting group description:	
radiation therapy 54Gy and concomitant capecitabine	
Reporting group title	second Randomization - B2 - Chemoradiotherapy
Reporting group description:	
Radiation therapy 54Gy and concomitant capecitabine. Then reintroduction of erlotinib alone 150mg per day until progression.	
Subject analysis set title	Second randomization - Chemotherapy
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
ARM B1 - gemcitabine plus erlotinib	
Subject analysis set title	Second randomization - Chemoradiotherapy
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
ARM B2 - radiation therapy 54Gy and concomitant capecitabine per os	

Primary: Overall survival on second randomization

End point title	Overall survival on second randomization[1]
End point description:	
In ITT2 population, 221 deaths had occurred—112 (82.4%) in the Chemotherapy arm and 109 (82.0%) in the Chemoradiotherapy arm. Median Overall Survival (OS) was 15.5 months (95% CI, 14.7 to 17.4 months) — 16.4 months (95% CI, 14.5 to 18.5 months) for Chemotherapy arm and 15.2 months (95% CI, 13.9 to 17.3 months) for Chemoradiotherapy arm. The HR was 1.03 (95% CI, 0.79 to 1.34; P= 0.83) — Result was not significant). The median follow-up was 36.7 months (CI 95% = [27.6; 44.2] months). Interaction test between the randomized arms at first and second randomization in ITT2 population was not significant (p=0.24).	
End point type	Primary
End point timeframe:	
From the date of the first randomization to the date of patient death, due to any cause, or to the last date the patient was known to be alive.	

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: The Kaplan-Meier method was used to evaluate overall survival in the ITT2 population. OS was calculated from the first randomization.
Comparisons on survival according to chemoradiatherapy or chemotherapy (Randomisation 2) were made with the log-rank test in the ITT2 population.
The 2 or the Fischer exact test was to be used, if necessary, for comparison of qualitative variables.
The Student t test will be used for quantitative variables.

End point values	Second randomization - Chemotherapy	Second randomization - Chemoradiotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	136	133		
Units: Months				
median (confidence interval 95%)	16.5 (14.5 to 18.5)	15.2 (13.9 to 17.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) on first randomization

End point title	Overall Survival (OS) on first randomization

End point description:

Patients who were not reported as dead at the time of the analysis were censored using the date they were known to be alive.
Among ITT1 population, the median follow-up was 34.3 months (CI 95%, 27.6 to 43.8months). There were 379 deaths at the end of follow-up. The median OS was 12.8 months (CI 95%, 11.8 to 14.1 months) — 13.6 months (95% CI, 12.3 to 15.3 months) for Gemcitabine arm and 11.9 months (95% CI, 10.4 to 13.5 months) for Gemcitabine + Erlotinib arm. The HR was 1.03 (95% CI, 0.79 to 1.34; P= 0.83) — log-rank test was borderline (p=0.09).

End point type	Secondary

End point timeframe:

From the date of the first randomization to the date of patient death, due to any cause, or to the last date the patient was known to be alive.

End point values	First randomization - Gemcitabine	First randomization - Gemcitabine plus Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	219		
Units: Months				
median (confidence interval 95%)	13.6 (12.3 to 15.3)	11.9 (10.4 to 13.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Death was regarded as a progression event in those patients who died before disease progression. Alive patients without documented objective progression at the time of the final analysis were censored at the

date of their last objective tumor assessment.

End point type	Secondary

End point timeframe:

Progression-free survival (PFS) was the time from the date of the first randomization to the date of progressive disease (RECIST 1.0 criteria) or death.

End point values	First randomization - Gemcitabine	First randomization - Gemcitabine plus Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	219		
Units: months				
median (confidence interval 95%)	7.8 (6.8 to 8.4)	6.5 (6 to 7.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) on second randomization

End point title	Progression free survival (PFS) on second randomization

End point description:

In ITT2 population, the median progression-free survival times were 11.8 months with chemotherapy and 12.5 months with Chemoradiotherapy. Progression events occurred in 123 patients receiving Chemotherapy and 118 receiving Chemoradiotherapy. The risk of progression was independent to treatment arms allocation (adjusted hazard ratio for Chemoradiotherapy, 0.9; 95% CI, 0.7 to 1.1; P = 0.22) (Figure 9). Similarly, in ITT1 population the log rank test was not significant (p=0.15). No interaction between the randomized arms was shown.

End point type	Secondary

End point timeframe:

Progression-free survival (PFS) was the time from the date of the first randomization to the date of progressive disease (RECIST 1.0 criteria) or death.

End point values	Second randomization - Chemotherapy	Second randomization - Chemoradiotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	122		
Units: months				
median (confidence interval 95%)	8.4 (7.8 to 9.4)	9.9 (8.8 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the randomization to the end of treatment	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15
Reporting groups	
Reporting group title	First randomization - Gemcitabine
Reporting group description: -	
Reporting group title	First randomization - Gemcitabine plus Erlotinib
Reporting group description: -	
Reporting group title	Second randomization - Chemotherapy
Reporting group description: -	
Reporting group title	Second randomization - Chemoradiotherapy
Reporting group description: -	

Serious adverse events	First randomization - Gemcitabine	First randomization - Gemcitabine plus Erlotinib	Second randomization - Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	77 / 223 (34.53%)	78 / 219 (35.62%)	38 / 136 (27.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inferior limb oedema			
subjects affected / exposed	0 / 223 (0.00%)	0 / 219 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Alteration of general status			
subjects affected / exposed	3 / 223 (1.35%)	6 / 219 (2.74%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anorexia			
subjects affected / exposed	1 / 223 (0.45%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 223 (0.00%)	2 / 219 (0.91%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bicytopenia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile epigastralgia			
subjects affected / exposed	0 / 223 (0.00%)	0 / 219 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	4 / 223 (1.79%)	11 / 219 (5.02%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
diabetes decompensation			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphonia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnea			
subjects affected / exposed	3 / 223 (1.35%)	2 / 219 (0.91%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic pain			
subjects affected / exposed	2 / 223 (0.90%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumopathy			
subjects affected / exposed	2 / 223 (0.90%)	1 / 219 (0.46%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
confusion			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arm fracture			
subjects affected / exposed	0 / 223 (0.00%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Break left coxa			

subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cardiac arrhythmia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac infarction			
subjects affected / exposed	1 / 223 (0.45%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
cerebal bleeding			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	5 / 223 (2.24%)	3 / 219 (1.37%)	3 / 136 (2.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal peritonitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute lithiasic cholecystitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pancreatitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angiocholitis			
subjects affected / exposed	5 / 223 (2.24%)	1 / 219 (0.46%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary Prothesis occlusion			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary stenosis			
subjects affected / exposed	0 / 223 (0.00%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowel obstruction			

subjects affected / exposed	0 / 223 (0.00%)	0 / 219 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 223 (0.00%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 223 (0.00%)	2 / 219 (0.91%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Digestive hemorragia			
subjects affected / exposed	2 / 223 (0.90%)	0 / 219 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fissurectomy			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
mesenteric infarctus			
subjects affected / exposed	0 / 223 (0.00%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 223 (1.35%)	3 / 219 (1.37%)	6 / 136 (4.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute cholangitis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 219 (0.46%)	4 / 136 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary prothesis replacement			
subjects affected / exposed	1 / 223 (0.45%)	1 / 219 (0.46%)	0 / 136 (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
Cholecystitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choledochus compression			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bile duct dilatation			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
icterus			
subjects affected / exposed	2 / 223 (0.90%)	0 / 219 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Cutaneous eruption			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis			
subjects affected / exposed	1 / 223 (0.45%)	3 / 219 (1.37%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute hepatitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sepsis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aplasia febrile			
subjects affected / exposed	0 / 223 (0.00%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilateral erysipelas			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatic cirrhose decompensation			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile syndrom			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infection			
subjects affected / exposed	2 / 223 (0.90%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
dehydratation			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 223 (0.00%)	0 / 219 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Second randomization - Chemoradiotherapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 133 (29.32%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inferior limb oedema			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Alteration of general status			
subjects affected / exposed	3 / 133 (2.26%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anorexia			

subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	3 / 133 (2.26%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bicytopenia				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile epigastralgia				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperthermia				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
diabetes decompensation				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				

Acute pulmonary oedema				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphonia				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnea				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thoracic pain				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumopathy				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
confusion				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Arm fracture				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Break left coxa				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
cardiac arrhythmia			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac infarction			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
cerebal bleeding			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 133 (3.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal peritonitis			

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute lithiasic cholecystitis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute pancreatitis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angiocholitis			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary Prothesis occlusion			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary stenosis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bowel obstruction			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			

subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Digestive hemorragia				
subjects affected / exposed	3 / 133 (2.26%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fissurectomy				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
mesenteric infarctus				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 133 (2.26%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 133 (1.50%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Acute cholangitis				

subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Biliary prothesis replacement				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Choledochus compression				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
bile duct dilatation				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
icterus				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Cutaneous eruption				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

Cystitis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acute hepatitis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute sepsis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aplasia febrile			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bilateral erysipelas			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
hepatic cirrhose decompensation			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile syndrom			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

dehydratation			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	First randomization - Gemcitabine	First randomization - Gemcitabine plus Erlotinib	Second randomization - Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	220 / 223 (98.65%)	219 / 219 (100.00%)	136 / 136 (100.00%)
Blood and lymphatic system disorders			
Neutrophil count	Additional description: Grade 3 - 4		
subjects affected / exposed	70 / 223 (31.39%)	78 / 219 (35.62%)	8 / 136 (5.88%)
occurrences (all)	0	0	0
Platelet count	Additional description: Grade 3 - 4		
subjects affected / exposed	3 / 223 (1.35%)	7 / 219 (3.20%)	3 / 136 (2.21%)
occurrences (all)	0	0	0
anemia	Additional description: Grade 3 - 4		
subjects affected / exposed	5 / 223 (2.24%)	13 / 219 (5.94%)	1 / 136 (0.74%)
occurrences (all)	0	0	0
Febrile neutropenia	Additional description: Grade 3 - 4		
subjects affected / exposed	0 / 223 (0.00%)	5 / 219 (2.28%)	0 / 136 (0.00%)
occurrences (all)	0	0	0
Aspartate transaminase	Additional description: Grade 3 - 4		
subjects affected / exposed	20 / 223 (8.97%)	22 / 219 (10.05%)	5 / 136 (3.68%)
occurrences (all)	0	0	0
Alanine aminotransferase	Additional description: Grade 3 - 4		
subjects affected / exposed	35 / 223 (15.70%)	30 / 219 (13.70%)	6 / 136 (4.41%)
occurrences (all)	0	0	0
Alkaline phosphatase			

subjects affected / exposed	22 / 223 (9.87%)	16 / 219 (7.31%)	4 / 136 (2.94%)
occurrences (all)	0	0	0
Bilirubin	Additional description: Grade 3 - 4		
subjects affected / exposed	11 / 223 (4.93%)	11 / 219 (5.02%)	5 / 136 (3.68%)
occurrences (all)	0	0	0
Gamma-glutamyltranspetidase	Additional description: Grade 3 - 4		
subjects affected / exposed	64 / 223 (28.70%)	46 / 219 (21.00%)	14 / 136 (10.29%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea	Additional description: Grade 3 - 4		
subjects affected / exposed	6 / 223 (2.69%)	7 / 219 (3.20%)	0 / 136 (0.00%)
occurrences (all)	0	0	0
Vomiting	Additional description: Grade 3 - 4		
subjects affected / exposed	3 / 223 (1.35%)	6 / 219 (2.74%)	0 / 136 (0.00%)
occurrences (all)	0	0	0
Diarrhea	Additional description: Grade 3 - 4		
subjects affected / exposed	3 / 223 (1.35%)	14 / 219 (6.39%)	1 / 136 (0.74%)
occurrences (all)	0	0	0
Infections and infestations			
Fever	Additional description: Grade 3 - 4		
subjects affected / exposed	2 / 223 (0.90%)	1 / 219 (0.46%)	0 / 136 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Second randomization - Chemoradiotherapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	133 / 133 (100.00%)		
Blood and lymphatic system disorders			
Neutrophil count	Additional description: Grade 3 - 4		
subjects affected / exposed	3 / 133 (2.26%)		
occurrences (all)	0		
Platelet count	Additional description: Grade 3 - 4		
subjects affected / exposed	0 / 133 (0.00%)		
occurrences (all)	0		
anemia	Additional description: Grade 3 - 4		
subjects affected / exposed	1 / 133 (0.75%)		
occurrences (all)	0		

Febrile neutropenia	Additional description: Grade 3 - 4		
subjects affected / exposed	0 / 133 (0.00%)		
occurrences (all)	0		
Aspartate transaminase	Additional description: Grade 3 - 4		
subjects affected / exposed	0 / 133 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase	Additional description: Grade 3 - 4		
subjects affected / exposed	2 / 133 (1.50%)		
occurrences (all)	0		
Alkaline phosphatase			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences (all)	0		
Bilirubin	Additional description: Grade 3 - 4		
subjects affected / exposed	2 / 133 (1.50%)		
occurrences (all)	0		
Gamma-glutamyltranspetidase	Additional description: Grade 3 - 4		
subjects affected / exposed	12 / 133 (9.02%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea	Additional description: Grade 3 - 4		
subjects affected / exposed	6 / 133 (4.51%)		
occurrences (all)	0		
Vomiting	Additional description: Grade 3 - 4		
subjects affected / exposed	3 / 133 (2.26%)		
occurrences (all)	0		
Diarrhea	Additional description: Grade 3 - 4		
subjects affected / exposed	5 / 133 (3.76%)		
occurrences (all)	0		
Infections and infestations			
Fever	Additional description: Grade 3 - 4		
subjects affected / exposed	1 / 133 (0.75%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2007	- Treatment delayed for more than 14 days for patients receiving gemcitabine alone or in association with erlotinib. - When toxicity is due to radiotherapy with a stop more than 7 consecutive days, except for patients who did already receive 5 consecutive weeks of radiotherapy who stop the treatment but remain included in the study - In case of early recurrence, added mention on the recommendation of the use of second-line FOLFOX
09 September 2008	to add the ancillary study (CirCé)
23 February 2009	to add exclusion criteria : ampulloma
15 April 2010	Statistical part revised, definition of two ITT populations
31 October 2011	Statistical section revised with intermediate analysis after 196 death events instead of 257

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.

In this trial in patients with disease controlled after 4 months of induction chemotherapy, there was no significant difference in overall survival of chemoradiotherapy compared to chemotherapy alone.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27139057