Clinical trial results:
phase IIb randomized clinical trial to evaluate the effectiveness of Gemcitabine-Erlotinib vs Gemcitabine-Erlotinib-Capecitabine in patients with metastatic pancreatic cancer.

Summary

EudraCT number	2010-022599-30
Trial protocol	ES
Global end of trial date	08 August 2016

Results information

Result version number	v1 (current)
This version publication date	08 September 2018
First version publication date	08 September 2018
Summary attachment (see zip file)	Manuscript EJC (2017 EJC GECA.pdf)

Trial information

Trial identification

Sponsor protocol code	TTD-10-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Grupo de tratamiento de los Tumores Digestivos
Sponsor organisation address	Téllez 30, madrid, Spain, 28007
Public contact	Sonia Maciá Escalante, Pivotal, 34 917081250, sonia.macia@pivotal.es
Scientific contact	Inmaculada Ruiz Mena, Grupo de Tratamiento de los Tumores Digestivos, 34 913788275, ttd@ttdgroup.org

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	29 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2016
Global end of trial reached?	Yes
Global end of trial date	08 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Progression free survival

Protection of trial subjects:

Treatment dose was adjusted in terms of adverse events and weight lose.
G-CSF was allowed as prophylaxis.
Adjuvant treatment for nausea/vomiting was prescribed if necessary.
Symptomatic treatment was recommended for other toxicities including diarrhea or skin toxicity.

Background therapy:

Gemcitabine has been established since its introduction as the standard first-line treatment in patients with locally advanced or metastatic pancreatic cancer. The experience accumulated in the treatment with gemcitabine in patients with pancreatic cancer indicates that the effects of treatment are moderate, with an average survival that varies from 5 to 8 months and survival rates after the first year of treatment of 17-25%.
In order to improve the therapeutic efficacy in patients with pancreatic cancer, numerous clinical trials have addressed this issue through the use of treatment regimens based on gemcitabine combined with a second cytotoxic agent.

Evidence for comparator:

Combination of gemcitabine with erlotinib in patients with advanced pancreatic cancer showed statistically significant improvements, compared to treatment with gemcitabine monotherapy, in overall survival, progression-free survival and survival 1 year.
In studies based on capecitabine, administered in different schedules: in monotherapy, in combination with gemcitabine, in combination with erlotinib or in combination with erlotinib + gemcitabine, efficacy data and a good toxicity profile were obtained in the treatment of cancer patients of advanced pancreas.
Considering the mentioned results (combination of erlotinib + gemcitabine + capecitabine could suppose an improvement in the efficacy of the treatment of patients with advanced pancreatic cancer with respect to the treatments currently available) this randomized phase IIb clinical trial was proposed, and based on the results of the NCIC CTG PA.3 study, the control group will be patients treated with gemcitabine + erlotinib.

Actual start date of recruitment	11 April 2011
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	Spain: 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)	100
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

120 patients were included; two out of them did not receive any study treatment. ITT included 60 patients at each arm, safety population included 60 patients at control arm and 58 at experimental arm. This was a national study with all patients being included at 23 Spanish sites.

Pre-assignment

Screening details:

Inclusion criteria:
Ability to understand and willingness to sign and give written informed consent, age ≥ 18 years, ECOG 0-2, life expectancy of at least 12 weeks, Patients with metastatic pancreatic adenocarcinoma, measurable disease, not having received previous systemic treatments, good organic function.

Period 1

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

Blinding implementation details:

Not applicable, open label study

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Gemcitabine plus erlotinib (G(1000 mg/m2, d1,8,15)+E(100 mg, d1–28)

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

Dosage and administration details:

1000 mg/m2 days 1, 8 and 15 every 28 days

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

Dosage and administration details:

100 mg, days 1-28

Arm title	Arm B

Arm description:

Experimental arm, G(1000 mg/m2, d1,8,15)+E(100 mg, d1–28)+C(1660 mg/m2, d1-21)

Arm type	Experimental
Investigational medicinal product name	gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details: 1000 mg/m2	
Investigational medicinal product name	erlotinib
Investigational medicinal product code	
Other name	tarceva
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 100 mg	
Investigational medicinal product name	capecitabine
Investigational medicinal product code	
Other name	xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 850 mg	

Number of subjects in period 1	Control	Arm B
Started	60	60
Completed	60	58
Not completed	0	2
Adverse event, non-fatal	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
120 pts were randomized. Median age: 63years; ECOG status0/1/2(%), 33/58/8. 52 women, 68 men. Median weight 67,26 Kg. Median body surface 1,72. Medican time from diagnosis 0,59 months. Diagnosis by histology in 57 patients; citology in 63 patients. Tx in 46 patients; T4 in 29 patients. All patients with metastatic disease. Median metastases location sites 3 (min-max; 1-9). Most common metastases locations: liver (93), regional lymph nodes (54), lung (24), distant lymph nodes (18), omentum (15)	

Reporting group values	Baseline	Total	
Number of subjects	120	120	
Age categorical			
Mean age was 61.33, median age 62.50. Min age was 29; maximum age 78			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	90	90	
From 65-84 years	30	30	
85 years and over	0	0	
Age continuous			
age for ITT population			
Units: years			
median	61		
inter-quartile range (Q1-Q3)	56 to 69	-	
Gender categorical			
Units: Subjects			
Female	52	52	
Male	68	68	

Subject analysis sets

Subject analysis set title	control arm
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
subjects included at control arm, 26 women and 34 men	
Subject analysis set title	experimental arm
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
experimental arm, 26 women and 34 men	

Reporting group values	control arm	experimental arm	
Number of subjects	60	60	
Age categorical			
Mean age was 61.33, median age 62.50. Min age was 29; maximum age 78			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	40	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous			
age for ITT population			
Units: years			
median	64	62	
inter-quartile range (Q1-Q3)	57 to 70	53 to 68	
Gender categorical			
Units: Subjects			
Female	26	26	
Male	34	34	

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Gemcitabine plus erlotinib (G(1000 mg/m2, d1,8,15)+E(100 mg, d1–28)	
Reporting group title	Arm B
Reporting group description:	
Experimental arm, G(1000 mg/m2, d1,8,15)+E(100 mg, d1–28)+C(1660 mg/m2, d1-21)	
Subject analysis set title	control arm
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
subjects included at control arm, 26 women and 34 men	
Subject analysis set title	experimental arm
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
experimental arm, 26 women and 34 men	

Primary: Progression free survival

End point title	Progression free survival
End point description:	
Time from inclusion until the date on which the disease progression or death from any cause is documented (whichever occurs first).	
End point type	Primary
End point timeframe:	
From inclusion until progressive disease	

End point values	Control	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[1]	60		
Units: months				
median PFS	3	4		

Notes:

[1] - 60 patients were included at arm A

Statistical analyses

Statistical analysis title	efficacy analysis

Statistical analysis description:

Primary endpoint is progression-free survival defined as the time from the randomization date to the patient's progression or death from any cause, whichever occurs first. Survival (progression-free and global) in each treatment arm with a Kaplan-Meier life table is described. Median survival is presented for each treatment group with their respective 95% confidence intervals.
The analysis between both arms was carried out through the Log-rank test stratified by ECOG.

Comparison groups	Control v Arm B

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.05 [3]
Method	Logrank
Parameter estimate	Median difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	5.6
Dispersion value	0.36

Notes:

[2] - A Cox model was applied to control other prognostic factors, after verifying the assumptions of proportionality through Schoenfeld residuals.
In these survival analyzes:
• Subjects in whom no evaluations of the tumor are available after the baseline assessment, but who remain alive at the deadline for collection of clinical data were censored on day 1 for SLP and on the date of last contact for SG.
• Subjects who have not manifested progression of the disease or who have died were censored.
[3] - Median survival is presented for each treatment group with their respective 95% confidence intervals.

Statistical analysis title	PFS depending on rash grade

Statistical analysis description:

PFS was analyzed depending on the rash grade that patients had presented while on treatment

Comparison groups	Control v Arm B
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Hazard ratio (HR)
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	11.9
Variability estimate	Standard deviation

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Since randomization till death due to any reason

End point values	Control	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: months				
median (standard deviation)				
Overall survival	7.7 (± 0.5)	6.8 (± 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Best objective response according to RECIST 1.1

End point type	Secondary

End point timeframe:

Since first patient in until end of study

End point values	Control	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: patients	11	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs were collected from first patient included (inform consent form signed) until 30 days after last study drug dose was administered	
Adverse event reporting additional description:	
A total of 34 patients (57%) in the GE arm and 42 patients (72%) in the GEC arm had grade 3 adverse events related to treatment. Treatment discontinuation due to treatment related adverse events occurred in eight patients in both the GE arm (13%)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	3

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Control arm	
Reporting group title	Arm B
Reporting group description:	
experimental arm	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 60 (53.33%)	25 / 58 (43.10%)	
number of deaths (all causes)	53	53	
number of deaths resulting from adverse events	7	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
tumor pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
progressive disease			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pulmonary embolism			

subjects affected / exposed	2 / 60 (3.33%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 60 (1.67%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ischemia periferal			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
General disorders and administration site conditions			
Ascites			
subjects affected / exposed	2 / 60 (3.33%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fever			
subjects affected / exposed	5 / 60 (8.33%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 60 (3.33%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 60 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer			

subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cholangitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
dyspnea			
subjects affected / exposed	1 / 60 (1.67%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
weakness			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Diverticulitis			

subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
staphilococcus positive			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
testis oedema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic oil syndrome			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
brain stroke			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
febril neutropaenia			

subjects affected / exposed	2 / 60 (3.33%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 60 (3.33%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 60 (5.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 60 (3.33%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowel movement irregularity			
subjects affected / exposed	0 / 60 (0.00%)	2 / 58 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epigastric discomfort			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic enteritis			

subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastric haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Acute abdomen			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Rectal haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal hemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatobiliary disorders			
Pain			
subjects affected / exposed	1 / 60 (1.67%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	3 / 60 (5.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilirubin conjugated increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 60 (1.67%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 60 (3.33%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis infective			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			

subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 60 (100.00%)	58 / 58 (100.00%)	
Vascular disorders			
Cough			
subjects affected / exposed	0 / 60 (0.00%)	3 / 58 (5.17%)	
occurrences (all)	0	3	
Embolism			
subjects affected / exposed	5 / 60 (8.33%)	3 / 58 (5.17%)	
occurrences (all)	5	3	
Phlebitis			
subjects affected / exposed	2 / 60 (3.33%)	4 / 58 (6.90%)	
occurrences (all)	2	4	
Surgical and medical procedures			
Alopecia			
subjects affected / exposed	2 / 60 (3.33%)	5 / 58 (8.62%)	
occurrences (all)	2	5	
Skin toxicity			
subjects affected / exposed	1 / 60 (1.67%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	41 / 60 (68.33%)	47 / 58 (81.03%)	
occurrences (all)	41	47	
pirexia			

subjects affected / exposed	28 / 60 (46.67%)	24 / 58 (41.38%)	
occurrences (all)	18	24	
Mucosal inflammation			
subjects affected / exposed	13 / 60 (21.67%)	24 / 58 (41.38%)	
occurrences (all)	13	24	
Oedema peripheral			
subjects affected / exposed	13 / 60 (21.67%)	12 / 58 (20.69%)	
occurrences (all)	13	12	
Pain			
subjects affected / exposed	9 / 60 (15.00%)	7 / 58 (12.07%)	
occurrences (all)	9	7	
General physical health deterioration			
subjects affected / exposed	4 / 60 (6.67%)	6 / 58 (10.34%)	
occurrences (all)	4	6	
Xerosis			
subjects affected / exposed	3 / 60 (5.00%)	3 / 58 (5.17%)	
occurrences (all)	3	3	
Oedema			
subjects affected / exposed	3 / 60 (5.00%)	1 / 58 (1.72%)	
occurrences (all)	3	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 60 (0.00%)	3 / 58 (5.17%)	
occurrences (all)	0	3	
Social circumstances			
Skin fissures			
subjects affected / exposed	2 / 60 (3.33%)	4 / 58 (6.90%)	
occurrences (all)	2	4	
Xeroderma			
subjects affected / exposed	0 / 60 (0.00%)	5 / 58 (8.62%)	
occurrences (all)	0	5	
Reproductive system and breast disorders			
Back pain			
subjects affected / exposed	10 / 60 (16.67%)	10 / 58 (17.24%)	
occurrences (all)	10	10	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	7 / 60 (11.67%)	4 / 58 (6.90%)	
occurrences (all)	7	4	
Epistaxis			
subjects affected / exposed	4 / 60 (6.67%)	3 / 58 (5.17%)	
occurrences (all)	4	3	
Rhinitis			
subjects affected / exposed	2 / 60 (3.33%)	3 / 58 (5.17%)	
occurrences (all)	2	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 60 (11.67%)	3 / 58 (5.17%)	
occurrences (all)	7	3	
Insomnia			
subjects affected / exposed	3 / 60 (5.00%)	4 / 58 (6.90%)	
occurrences (all)	3	4	
Investigations			
GGT increased			
subjects affected / exposed	17 / 60 (28.33%)	5 / 58 (8.62%)	
occurrences (all)	17	5	
Alanine aminotransferase increased			
subjects affected / exposed	7 / 60 (11.67%)	2 / 58 (3.45%)	
occurrences (all)	7	2	
Weight decreased			
subjects affected / exposed	5 / 60 (8.33%)	4 / 58 (6.90%)	
occurrences (all)	5	4	
alkaline phosphatase increased			
subjects affected / exposed	5 / 60 (8.33%)	3 / 58 (5.17%)	
occurrences (all)	5	3	
Transaminases increased			
subjects affected / exposed	3 / 60 (5.00%)	3 / 58 (5.17%)	
occurrences (all)	3	3	
Bilirubin conjugated increased			
subjects affected / exposed	5 / 60 (8.33%)	1 / 58 (1.72%)	
occurrences (all)	5	1	
Aspartate aminotransferase increased			

subjects affected / exposed	5 / 60 (8.33%)	1 / 58 (1.72%)	
occurrences (all)	5	1	
Nervous system disorders			
Cachexia			
subjects affected / exposed	2 / 60 (3.33%)	3 / 58 (5.17%)	
occurrences (all)	2	3	
Dysgeusia			
subjects affected / exposed	2 / 60 (3.33%)	4 / 58 (6.90%)	
occurrences (all)	2	4	
Dizziness			
subjects affected / exposed	3 / 60 (5.00%)	3 / 58 (5.17%)	
occurrences (all)	3	3	
Paraesthesia			
subjects affected / exposed	4 / 60 (6.67%)	1 / 58 (1.72%)	
occurrences (all)	4	1	
Somnolence			
subjects affected / exposed	2 / 60 (3.33%)	3 / 58 (5.17%)	
occurrences (all)	2	3	
Headache			
subjects affected / exposed	1 / 60 (1.67%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	21 / 60 (35.00%)	36 / 58 (62.07%)	
occurrences (all)	21	36	
anemia			
subjects affected / exposed	21 / 60 (35.00%)	29 / 58 (50.00%)	
occurrences (all)	21	29	
Thrombocytopenia			
subjects affected / exposed	19 / 60 (31.67%)	30 / 58 (51.72%)	
occurrences (all)	19	30	
Leukopenia			
subjects affected / exposed	3 / 60 (5.00%)	5 / 58 (8.62%)	
occurrences (all)	3	5	
Gastrointestinal disorders			

Fatigue			
subjects affected / exposed	3 / 60 (5.00%)	0 / 58 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	28 / 60 (46.67%)	37 / 58 (63.79%)	
occurrences (all)	28	37	
Nausea			
subjects affected / exposed	29 / 60 (48.33%)	30 / 58 (51.72%)	
occurrences (all)	29	30	
Vomiting			
subjects affected / exposed	25 / 60 (41.67%)	24 / 58 (41.38%)	
occurrences (all)	25	24	
Constipation			
subjects affected / exposed	19 / 60 (31.67%)	25 / 58 (43.10%)	
occurrences (all)	19	25	
Abdominal pain			
subjects affected / exposed	18 / 60 (30.00%)	24 / 58 (41.38%)	
occurrences (all)	18	24	
Abdominal pain upper			
subjects affected / exposed	9 / 60 (15.00%)	13 / 58 (22.41%)	
occurrences (all)	9	13	
Dyspepsia			
subjects affected / exposed	7 / 60 (11.67%)	6 / 58 (10.34%)	
occurrences (all)	7	6	
Dry mouth			
subjects affected / exposed	7 / 60 (11.67%)	4 / 58 (6.90%)	
occurrences (all)	7	4	
Abdominal distension			
subjects affected / exposed	4 / 60 (6.67%)	6 / 58 (10.34%)	
occurrences (all)	4	6	
Ascites			
subjects affected / exposed	4 / 60 (6.67%)	3 / 58 (5.17%)	
occurrences (all)	4	3	
Flatulence			
subjects affected / exposed	3 / 60 (5.00%)	3 / 58 (5.17%)	
occurrences (all)	3	3	

Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	5 / 60 (8.33%)	4 / 58 (6.90%)	
occurrences (all)	5	4	
Cholangitis			
subjects affected / exposed	0 / 60 (0.00%)	3 / 58 (5.17%)	
occurrences (all)	0	3	
Liver function test abnormal			
subjects affected / exposed	3 / 60 (5.00%)	0 / 58 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	30 / 60 (50.00%)	28 / 58 (48.28%)	
occurrences (all)	30	28	
Palmoplantar keratoderma			
subjects affected / exposed	2 / 60 (3.33%)	13 / 58 (22.41%)	
occurrences (all)	2	13	
Dry skin			
subjects affected / exposed	1 / 60 (1.67%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
Onycholysis			
subjects affected / exposed	0 / 60 (0.00%)	3 / 58 (5.17%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	4 / 60 (6.67%)	2 / 58 (3.45%)	
occurrences (all)	4	2	
Musculoskeletal and connective tissue disorders			
limb pain			
subjects affected / exposed	3 / 60 (5.00%)	3 / 58 (5.17%)	
occurrences (all)	3	3	
Arthralgia			
subjects affected / exposed	1 / 60 (1.67%)	5 / 58 (8.62%)	
occurrences (all)	1	5	
muscle pain			

subjects affected / exposed	2 / 60 (3.33%)	3 / 58 (5.17%)	
occurrences (all)	2	3	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 60 (6.67%)	6 / 58 (10.34%)	
occurrences (all)	4	6	
Cellulitis			
subjects affected / exposed	3 / 60 (5.00%)	2 / 58 (3.45%)	
occurrences (all)	3	2	
Paronychia			
subjects affected / exposed	1 / 60 (1.67%)	3 / 58 (5.17%)	
occurrences (all)	1	3	
Conjunctivitis			
subjects affected / exposed	4 / 60 (6.67%)	0 / 58 (0.00%)	
occurrences (all)	4	0	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	29 / 60 (48.33%)	30 / 58 (51.72%)	
occurrences (all)	29	30	
Hyperglycaemia			
subjects affected / exposed	5 / 60 (8.33%)	4 / 58 (6.90%)	
occurrences (all)	5	4	
Hypoglycaemia			
subjects affected / exposed	0 / 60 (0.00%)	3 / 58 (5.17%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 January 2012	A new exploratory objective was added (peripheral blood analysis to search predictive biomarkers)
24 March 2014	Trial end date was updated, as "End of trial will be the date when last patient finishes treatment phase due to any reason and after End of Study or early withdrawal visit is performed"

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.

The delivered dose intensity of both gemcitabine and erlotinib being lower in the GEC arm, primarily as a result of haematological toxicities; this might explain the treatment with GEC was less effective than expected

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28222309