Clinical trial results:
Selecting Treatment in Colorectal Cancer: Capecitabine or 5-fluorouracil Selection to be Combined With Oxaliplatin or Irinotecan as First-line Chemotherapy in Advanced Colorectal Cancer (SETICC)

Summary

EudraCT number	2009-012562-31
Trial protocol	ES
Global end of trial date	07 November 2013

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020

Trial information

Trial identification

Sponsor protocol code	TTD-09-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01071655
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo de Tratamiento de los Tumores Digestivos (TTD)
Sponsor organisation address	Plaza de Castilla, 3, 8º D- 1., Madrid, Spain, 28046
Public contact	Inmaculada Ruiz Mena, Grupo de Tratamiento de los Tumores Digestivos (TTD), 0034 913788275, ttd@ttdgroup.org
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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	30 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2013
Global end of trial reached?	Yes
Global end of trial date	07 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the present study was to examine whether assigning first-line chemotherapy based on relevant germline polymorphisms would improve outcomes compared with treating all patients with a standard regimen.

The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), overall response rate (ORR; assessed using RECIST Version 1.1), proportion of patients whose disease became resectable, adverse events, and evaluation of KRAS exon 2 mutation status as a molecular prognostic marker.

Protection of trial subjects:

Treatment was assigned depending on TYMS-3'UTR 6 bp ins/del and ERCC1-118C/T polymorphisms. Investigators were informed of treatments by automatically generated e-mails. Polymorphisms were determined for patients assigned to the control group, but these results were not needed before treatment commenced. The investigator still received an automatically generated e-mail. Treatment continued until disease progression, unacceptable toxicity, or patient withdrawal.

Background therapy:

Patients assigned to the control group received bevacizumab 7.5 mg/kg on day 1 with XELOX.

Evidence for comparator:

Our previous study suggested that patients harboring the TYMS-30 untranslated region (UTR) 6 bp ins/ins and ERCC1-118C/T or C/C genotypes might benefit from combining oxaliplatin with capecitabine rather than 5-FU.

Actual start date of recruitment	15 February 2010
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: 195
Worldwide total number of subjects	195
EEA total number of subjects	195

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)	105
From 65 to 84 years	88
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Of 202 patients enrolled, 195 were treated/randomized. There were 7 screening failures (withdrawn consent, n=1; criteria violation, n=6). This was a national study with all patients being included at 31 Spanish sites.

Pre-assignment

Screening details:

Adult patients (≥18 years) with histologically confirmed colon or rectal adenocarcinoma with measurable metastatic disease, ECOG performance status 0–2, and adequate renal function. Key exclusion criteria: prior systemic treatment of metastatic disease; concomitant CVD; CNS disease, uncontrolled hypertension, bleeding diathesis, or coagulopathy.

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.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Group (A) (Bev+XELOX)

Arm description:

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the control group received bevacizumab 7.5 mg/kg on day 1 with XELOX (capecitabine 1000 mg/m2/12 h days 1-14, and oxaliplatin 130 mg/m2 on day 1). One cycle corresponds to 3 weeks of treatment.

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 7.5 mg/kg on day 1.

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

Dosage and administration details:

Capecitabine 1000 mg/m2/12 h on days 1-14

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin 130 mg/m2 on day 1

Arm title	Experimental Group (B)

Arm description:

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the experimental group received different schedules according to the number of TYMS-3'UTR 6 bp ins/del and ERCC1-118C/T favorable genotypes:

1) Patients with no favorable genotypes (FG) (Bev+XELIRI);
2) Patients with one FG: TS 3'UTR +6bp/+6bp and ERCC1-118 T/T (Bev+XELOX); TS 3'UTR +6bp/-6bp and ERCC1-118 C/T or C/C (Bev+FUIRI);
3) Patients with two FG (Bev+FUOX).

Arm type	Experimental
Investigational medicinal product name	Bev+XELIRI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bevacizumab 7.5 mg/kg on day 1 with XELIRI (capecitabine 800 mg/m2/12 h days 1-14, and irinotecan 200 mg/m2 on day 1). One cycle corresponds to 3 weeks of treatment.

Investigational medicinal product name	Bev+XELOX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bevacizumab 7.5 mg/kg on day 1 with XELOX (capecitabine 1000 mg/m2/12 h days 1-14, and oxaliplatin 130 mg/m2 on day 1). One cycle corresponds to 3 weeks of treatment.

Investigational medicinal product name	Bev+FUIRI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 5 mg/kg (days 1, 15 and 29) with FUIRI (5-FU 2.250 mg/m2 in 48h-continuous infusion and irinotecan 80 mg/m2 on days 1, 8, 15, 22, 29 and 36). One cycle corresponds to 6 weeks of treatment.

Investigational medicinal product name	Bev+FUOX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 5 mg/kg (days 1, 15 and 29) with FUOX (5-FU 2.250 mg/m2 in 48h-continuous infusion on days 1, 8, 15, 22, 29 and 36; and oxaliplatin 85 mg/m2 on days 1, 15 and 29). One cycle corresponds to 6 weeks of treatment.

Number of subjects in period 1	Control Group (A) (Bev+XELOX)	Experimental Group (B)
Started	65	130
Completed	61	119
Not completed	4	11
Adverse event, serious fatal	4	3
Consent withdrawn by subject	-	4

Protocol deviation	-	4

Baseline characteristics

Reporting groups

Reporting group title	Control Group (A) (Bev+XELOX)

Reporting group description:

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the control group received bevacizumab 7.5 mg/kg on day 1 with XELOX (capecitabine 1000 mg/m2/12 h days 1-14, and oxaliplatin 130 mg/m2 on day 1). One cycle corresponds to 3 weeks of treatment.

Reporting group title	Experimental Group (B)

Reporting group description:

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the experimental group received different schedules according to the number of TYMS-3'UTR 6 bp ins/del and ERCC1-118C/T favorable genotypes:

1) Patients with no favorable genotypes (FG) (Bev+XELIRI);
2) Patients with one FG: TS 3'UTR +6bp/+6bp and ERCC1-118 T/T (Bev+XELOX); TS 3'UTR +6bp/-6bp and ERCC1-118 C/T or C/C (Bev+FUIRI);
3) Patients with two FG (Bev+FUOX).

Reporting group values	Control Group (A) (Bev+XELOX)	Experimental Group (B)	Total
Number of subjects	65	130	195
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age in years has been calculated the date of signing the informed consent			
Units: years			
arithmetic mean	64.4	63.4	
standard deviation	± 10.1	± 10.4	-
Gender categorical Units: Subjects			
Female	30	48	78
Male	35	82	117
ECOG performance status Units: Subjects			
ECOG 0	29	50	79
ECOG 1	34	79	113
ECOG 2	2	1	3
Tumor location Units: Subjects			
Colon	41	80	121
Rectum	18	38	56

Both	6	12	18
No. of affected organs Units: Subjects			
1 organ	25	55	80
2 organs	21	52	73
>2 organs	19	23	42
Surgery for primary tumor Units: Subjects			
Yes	34	73	107
No	31	57	88
Prior adjuvant radiotherapy			
With or without prior radiotherapy			
Units: Subjects			
Yes	3	7	10
No	62	123	185
KRAS mutation Units: Subjects			
Wild-type	31	64	95
Mutated	27	42	69
Not available	7	24	31
Relevant prior and concomitant pathologies Units: Subjects			
No	5	15	20
Yes	60	115	175
Prior adjuvant chemotherapy Units: Subjects			
Yes	9	15	24
No	56	115	171
Weight Units: kilogram(s)			
arithmetic mean	71.4	71.3	
standard deviation	± 12.2	± 14.8	-
Height Units: centimeters			
arithmetic mean	163.8	164.2	
standard deviation	± 8.6	± 10.2	-
Body surface Units: square meter			
arithmetic mean	1.8	1.8	
standard deviation	± 0.2	± 0.2	-
Duration of disease			
Time since diagnosis of primary disease until the date of signing the informed consent.			
Units: months			
arithmetic mean	10.1	5.7	
standard deviation	± 27.2	± 11.5	-

End points

End points reporting groups

Reporting group title	Control Group (A) (Bev+XELOX)

Reporting group description:

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the control group received bevacizumab 7.5 mg/kg on day 1 with XELOX (capecitabine 1000 mg/m2/12 h days 1-14, and oxaliplatin 130 mg/m2 on day 1). One cycle corresponds to 3 weeks of treatment.

Reporting group title	Experimental Group (B)

Reporting group description:

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the experimental group received different schedules according to the number of TYMS-3'UTR 6 bp ins/del and ERCC1-118C/T favorable genotypes:

1) Patients with no favorable genotypes (FG) (Bev+XELIRI);
2) Patients with one FG: TS 3'UTR +6bp/+6bp and ERCC1-118 T/T (Bev+XELOX); TS 3'UTR +6bp/-6bp and ERCC1-118 C/T or C/C (Bev+FUIRI);
3) Patients with two FG (Bev+FUOX).

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

Time elapsed from the randomization date until the patient progression or death for any reason (the first that occurred).

End point type	Primary

End point timeframe:

Until patient progression or death for any reason (the first that occurred)

End point values	Control Group (A) (Bev+XELOX)	Experimental Group (B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	130		
Units: months				
median (confidence interval 95%)	9.4 (6.8 to 12.1)	10.1 (8.5 to 11.6)		

Attachments (see zip file)	Progression-free survival/PFS.PNG

Statistical analyses

Statistical analysis title	Hazard ratio
Comparison groups	Control Group (A) (Bev+XELOX) v Experimental Group (B)

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.745
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.942
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.657
upper limit	1.351

Secondary: Overall surival

End point title	Overall surival

End point description:

Time elapsed from the randomization date until the patient death. In other patients the last control was considered the last follow-up available.

End point type	Secondary

End point timeframe:

Until patient death or the last follow-up available.

End point values	Control Group (A) (Bev+XELOX)	Experimental Group (B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	130		
Units: months				
median (confidence interval 95%)	16.5 (13.7 to 19.4)	19.1 (15.5 to 22.7)		

Attachments (see zip file)	Overall survival/OS.PNG

Statistical analyses

Statistical analysis title	Hazard ratio
Comparison groups	Control Group (A) (Bev+XELOX) v Experimental Group (B)
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.798
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.956

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.678
upper limit	1.348

Secondary: Complete response (CR)

End point title	Complete response (CR)

End point description:

End point type	Secondary

End point timeframe:

From treatment start to the decision to end

End point values	Control Group (A) (Bev+XELOX)	Experimental Group (B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[1]	106[2]		
Units: Subjects	2	4		

Notes:

[1] - Patients of the control group that were evaluable for response.

[2] - Patients of the experimental group that were evaluable for response.

Statistical analyses

No statistical analyses for this end point

Secondary: Partial response (PR)

End point title	Partial response (PR)

End point description:

End point type	Secondary

End point timeframe:

From treatment start to the decision to end

End point values	Control Group (A) (Bev+XELOX)	Experimental Group (B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[3]	106[4]		
Units: Subjects	24	65		

Notes:

[3] - Patients of the control group that were evaluable for response.

[4] - Patients of the experimental group that were evaluable for response.

Statistical analyses

No statistical analyses for this end point

Secondary: Stable disease

End point title	Stable disease

End point description:

End point type	Secondary

End point timeframe:

From treatment start to the decision to end

End point values	Control Group (A) (Bev+XELOX)	Experimental Group (B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[5]	106[6]		
Units: Subjects	22	30		

Notes:

[5] - Patients of the control group that were evaluable for response.

[6] - Patients of the experimental group that were evaluable for response.

Statistical analyses

No statistical analyses for this end point

Secondary: Progressive disease

End point title	Progressive disease

End point description:

End point type	Secondary

End point timeframe:

From treatment start to the decision to end

End point values	Control Group (A) (Bev+XELOX)	Experimental Group (B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[7]	106[8]		
Units: Subjects	7	7		

Notes:

[7] - Patients of the control group that were evaluable for response.

[8] - Patients of the experimental group that were evaluable for response.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) (PR+CR)

End point title	Overall response rate (ORR) (PR+CR)

End point description:

Partial response (PR) + Complete response (CR). It was assessed using RECIST Version 1.1

End point type	Secondary

End point timeframe:

From treatment start to the decision to end

End point values	Control Group (A) (Bev+XELOX)	Experimental Group (B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[9]	106[10]		
Units: Subjects	26	69		

Notes:

[9] - Patients of the control group that were evaluable for response.

[10] - Patients of the experimental group that were evaluable for response.

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	Control Group (A) (Bev+XELOX) v Experimental Group (B)
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.042
Method	Fisher exact

Secondary: Disease-control rate (CR+PR+SD)

End point title	Disease-control rate (CR+PR+SD)

End point description:

Complete response (CR) + Partial response (PR) + Stable disease (SD)

End point type	Secondary

End point timeframe:
From treatment start to the decision to end

End point values	Control Group (A) (Bev+XELOX)	Experimental Group (B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[11]	106[12]		
Units: Subjects	48	99		

Notes:
[11] - Patients of the control group that were evaluable for response.
[12] - Patients of the experimental group that were evaluable for response.

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	Control Group (A) (Bev+XELOX) v Experimental Group (B)
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.24
Method	Fisher exact

Secondary: R0 surgery

End point title	R0 surgery

End point description:

End point type	Secondary

End point timeframe:
During or after the study

End point values	Control Group (A) (Bev+XELOX)	Experimental Group (B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[13]	21[14]		
Units: Subjects	7	18		

Notes:
[13] - 16 patients of the control group with surgical resection
[14] - 21 patients of the experimental group with surgical resection

Statistical analyses

Statistical analysis title	Fisher exact
Comparison groups	Control Group (A) (Bev+XELOX) v Experimental Group (B)

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.018
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study period.

Adverse event reporting additional description:

An adverse event is reported once per patient and treatment period with the highest severity grade according to NCI-CTCAE version 3.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Group A - Safety population

Reporting group description:

Patients who have received at least one administration of study drug in Group A: BVZ+XELOX (Bevacizumab + capecitabine + oxaliplatin).

Reporting group title	Group B (global) - Safety population

Reporting group description:

Patients who have received at least one administration of study drug in Group B (global). Reported for all Group B subgroups in total (BVZ+XELOX/XELIRI/FUOX/FUIRI).

Serious adverse events	Group A - Safety population	Group B (global) - Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 61 (44.26%)	61 / 119 (51.26%)	
number of deaths (all causes)	49	97	
number of deaths resulting from adverse events	3	11	
Vascular disorders			
Acute pulmonary edema			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain vascular accident			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	1 / 61 (1.64%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematoma			
subjects affected / exposed	0 / 61 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thromboembolism			
subjects affected / exposed	2 / 61 (3.28%)	8 / 119 (6.72%)	
occurrences causally related to treatment / all	2 / 2	7 / 8	
deaths causally related to treatment / all	0 / 0	3 / 3	
Vein thrombosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Foot ischemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolemic shock			
subjects affected / exposed	0 / 61 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasospastic angina			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cognitive impairment			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertiginous syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Abdominal pain			
subjects affected / exposed	0 / 61 (0.00%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epigastralgy			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fever			
subjects affected / exposed	3 / 61 (4.92%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General deterioration			
subjects affected / exposed	0 / 61 (0.00%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar pain			
subjects affected / exposed	2 / 61 (3.28%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple myeloma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 61 (1.64%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Blood and lymphatic system disorders			
Aplasia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 61 (1.64%)	4 / 119 (3.36%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal bleeding			

subjects affected / exposed	1 / 61 (1.64%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocitopenia			
subjects affected / exposed	1 / 61 (1.64%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal bleeding			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abscess perianal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowel obstruction			
subjects affected / exposed	7 / 61 (11.48%)	5 / 119 (4.20%)	
occurrences causally related to treatment / all	0 / 7	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 61 (1.64%)	12 / 119 (10.08%)	
occurrences causally related to treatment / all	1 / 1	14 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bleeding			

subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal perforation			
subjects affected / exposed	1 / 61 (1.64%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 61 (1.64%)	4 / 119 (3.36%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hematemesis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	0 / 61 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction of bile duct anastomotic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parasigmoid abscess			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic duodenitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	3 / 61 (4.92%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
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			
Dyspnoea			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatobiliary disorders			
Hepatic veno oclusive disease			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic hepatitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor fistulization			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 61 (1.64%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	

Infections and infestations			
Bacterial meningitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Catheter infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep infection of intestinal fistula			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 61 (0.00%)	4 / 119 (3.36%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Fournier Gangrene			
subjects affected / exposed	0 / 61 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peristomal abscess			
subjects affected / exposed	1 / 61 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory infection			

subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical wound infection			
subjects affected / exposed	1 / 61 (1.64%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocapnia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive ictericia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group A - Safety population	Group B (global) - Safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 61 (100.00%)	118 / 119 (99.16%)	
Cardiac disorders			
Hypertension			
subjects affected / exposed	14 / 61 (22.95%)	23 / 119 (19.33%)	
occurrences (all)	20	24	
Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	22 / 61 (36.07%)	13 / 119 (10.92%)	
occurrences (all)	53	18	
Neuropathy			
subjects affected / exposed	39 / 61 (63.93%)	36 / 119 (30.25%)	
occurrences (all)	102	57	
Neurotoxicity			
subjects affected / exposed	9 / 61 (14.75%)	8 / 119 (6.72%)	
occurrences (all)	25	19	
Anxiety			
subjects affected / exposed	3 / 61 (4.92%)	7 / 119 (5.88%)	
occurrences (all)	3	8	
Dizziness			
subjects affected / exposed	2 / 61 (3.28%)	10 / 119 (8.40%)	
occurrences (all)	2	14	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 61 (21.31%)	30 / 119 (25.21%)	
occurrences (all)	21	54	
Neutropenia			
subjects affected / exposed	14 / 61 (22.95%)	27 / 119 (22.69%)	
occurrences (all)	40	72	
Thrombocytopenia			
subjects affected / exposed	15 / 61 (24.59%)	10 / 119 (8.40%)	
occurrences (all)	28	13	
Epistaxis			
subjects affected / exposed	12 / 61 (19.67%)	32 / 119 (26.89%)	
occurrences (all)	19	46	
Rectal bleeding			

subjects affected / exposed	7 / 61 (11.48%)	15 / 119 (12.61%)	
occurrences (all)	7	17	
Oedema			
subjects affected / exposed	7 / 61 (11.48%)	8 / 119 (6.72%)	
occurrences (all)	7	8	
Leukopenia			
subjects affected / exposed	3 / 61 (4.92%)	8 / 119 (6.72%)	
occurrences (all)	3	19	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	46 / 61 (75.41%)	90 / 119 (75.63%)	
occurrences (all)	117	280	
Common cold			
subjects affected / exposed	6 / 61 (9.84%)	9 / 119 (7.56%)	
occurrences (all)	8	11	
Fever			
subjects affected / exposed	12 / 61 (19.67%)	27 / 119 (22.69%)	
occurrences (all)	16	33	
Weight decreased			
subjects affected / exposed	5 / 61 (8.20%)	3 / 119 (2.52%)	
occurrences (all)	5	5	
Abdominal pain			
subjects affected / exposed	24 / 61 (39.34%)	42 / 119 (35.29%)	
occurrences (all)	38	54	
Anal pain			
subjects affected / exposed	4 / 61 (6.56%)	6 / 119 (5.04%)	
occurrences (all)	5	9	
Insomnia			
subjects affected / exposed	3 / 61 (4.92%)	10 / 119 (8.40%)	
occurrences (all)	3	10	
Back pain			
subjects affected / exposed	1 / 61 (1.64%)	6 / 119 (5.04%)	
occurrences (all)	2	7	
Lumbar pain			

subjects affected / exposed	3 / 61 (4.92%)	6 / 119 (5.04%)	
occurrences (all)	4	7	
Pain			
subjects affected / exposed	2 / 61 (3.28%)	6 / 119 (5.04%)	
occurrences (all)	2	7	
Gastrointestinal disorders			
Anorexia nervosa			
subjects affected / exposed	16 / 61 (26.23%)	32 / 119 (26.89%)	
occurrences (all)	32	53	
Bowel obstruction			
subjects affected / exposed	6 / 61 (9.84%)	3 / 119 (2.52%)	
occurrences (all)	6	3	
Constipation			
subjects affected / exposed	19 / 61 (31.15%)	30 / 119 (25.21%)	
occurrences (all)	30	46	
Diarrhoea			
subjects affected / exposed	43 / 61 (70.49%)	99 / 119 (83.19%)	
occurrences (all)	93	358	
Dysgeusia			
subjects affected / exposed	10 / 61 (16.39%)	18 / 119 (15.13%)	
occurrences (all)	15	28	
Hyporexia			
subjects affected / exposed	7 / 61 (11.48%)	16 / 119 (13.45%)	
occurrences (all)	11	24	
Mucositis			
subjects affected / exposed	23 / 61 (37.70%)	55 / 119 (46.22%)	
occurrences (all)	42	97	
Nausea			
subjects affected / exposed	28 / 61 (45.90%)	56 / 119 (47.06%)	
occurrences (all)	54	109	
Vomiting			
subjects affected / exposed	29 / 61 (47.54%)	51 / 119 (42.86%)	
occurrences (all)	67	130	
Xerostomy			
subjects affected / exposed	5 / 61 (8.20%)	6 / 119 (5.04%)	
occurrences (all)	6	7	

Gingivitis			
subjects affected / exposed	3 / 61 (4.92%)	7 / 119 (5.88%)	
occurrences (all)	3	10	
Tenesmus			
subjects affected / exposed	1 / 61 (1.64%)	6 / 119 (5.04%)	
occurrences (all)	1	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 61 (6.56%)	11 / 119 (9.24%)	
occurrences (all)	5	18	
Dyspnoea			
subjects affected / exposed	4 / 61 (6.56%)	8 / 119 (6.72%)	
occurrences (all)	6	9	
Skin and subcutaneous tissue disorders			
Hand-foot syndrome			
subjects affected / exposed	28 / 61 (45.90%)	34 / 119 (28.57%)	
occurrences (all)	52	71	
Hyperpigmentation			
subjects affected / exposed	6 / 61 (9.84%)	8 / 119 (6.72%)	
occurrences (all)	8	9	
Pruritus			
subjects affected / exposed	4 / 61 (6.56%)	9 / 119 (7.56%)	
occurrences (all)	5	9	
Alopecia			
subjects affected / exposed	2 / 61 (3.28%)	25 / 119 (21.01%)	
occurrences (all)	2	31	
Infections and infestations			
Respiratory infection			
subjects affected / exposed	4 / 61 (6.56%)	7 / 119 (5.88%)	
occurrences (all)	4	10	
Urinary tract infection			
subjects affected / exposed	5 / 61 (8.20%)	12 / 119 (10.08%)	
occurrences (all)	8	17	
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	1 / 61 (1.64%)	9 / 119 (7.56%)	
occurrences (all)	1	14	
Hyperglycaemia			
subjects affected / exposed	0 / 61 (0.00%)	8 / 119 (6.72%)	
occurrences (all)	0	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2009	Taking into account the suggestions of the research ethics committee to approve the study.
02 October 2009	Through this amendment 8 new centers have been added: H.San Juan Reus, C.H. Zamora, H. Josep Trueta, H.G.U. Gregorio Marañón, IDOC Corachan, H. Granollers, H. Guadalajara, H. Virgen Arrixaca.
23 October 2009	Correction of a typographic error regarding the administration regimens of the two drugs administered every 2 weeks (Bevacizumab and Oxaliplatin): arms of treatment with FUIRI and FUOX.
03 November 2009	Through this amendment one new center has been added (H. Puerta Hierro)
01 March 2010	Through this amendment some parts of the protocol have been modified /clarified, the biological study has been included and two new centers have been added: ICO and H. Doce de Octubre. Moreover, Dra Sandra Merino Varela replaced Dr Julen Fernandez as the Principal Investigator in H. Sant Joan de Reus.
01 April 2011	Through this amendment Dra Montserrat Gay Pastor replaced Miquel Nogué Aliguer as the Principal Investigator in Consorci Hospitalari de Vic.
17 January 2013	Through this amendment Dra Clara Montagut Viladot replaced Dr Manuel Gallén Castillo as the Principal Investigator in Hospital del Mar.
27 May 2013	Through this amendment Dr José Luis Manzano Mozo replaced Dr Albert Abad Esteve as the Principal Investigator in Hospital Germans Trias i Pujol.
16 July 2013	Through this amendment Dr Luis Robles Díaz replaced Dra Cristina Grávalos Castro as the Principal Investigator in Hospital Universitario 12 de Octubre.

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.

Serum samples were not analyzed for cell-free tumor DNA. This technique may allow identification of variability in response due to the tumor genome, complementary to information provided by examination of germline polymorphisms.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29145602