Clinical trial results:
Phase III, randomized clinical trial to evaluate FOLFOX + bebacizumab versus FOLFOXIRI + bebacizumab as first line treatment of patients with metastatic colorectal cancer not previously treated and with three or more circulating tumoral cells.

Summary

EudraCT number	2012-000846-37
Trial protocol	ES
Global end of trial date	30 November 2019

Results information

Result version number	v1 (current)
This version publication date	04 June 2021
First version publication date	04 June 2021

Trial information

Trial identification

Sponsor protocol code	TTD-12-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01640405
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo de Tratamiento de los Tumores Digestivos (TTD)
Sponsor organisation address	Téllez 30, Madrid, Spain, 28007
Public contact	Grupo de Tratamiento de los Tumores Digestivos (TTD), Grupo de Tratamiento de los Tumores Digestivos (TTD), 34 913788275, ttd@ttdgroup.org
Scientific contact	Grupo de Tratamiento de los Tumores Digestivos (TTD), Grupo de Tratamiento de los Tumores Digestivos (TTD), 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	10 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Progression free survival (PFS) efficacy compared between FOLFOX + Bevacizumab vs FOLFOXIRI + Bevacizumab, in mCRC first line treated patients with 3 or more Circulating tumor cells (CTC).

Protection of trial subjects:

Any medication that patients needed for their correct clinical control (except prohibited therapies), according to investigator's criteria were allowed.

Background therapy:

Sedative treatment, antiemetic treatment, antibiotics, analgesic treatment, antihistamines. antihyperpensive drugs, low doses of steroids, concentrates of erythrocytes, platelets or plasma coud be administered to contribute at treatment of pain, infection and other complications of the malignant neoplasm. In case of febrile neutropenia or documented infection, colony stimulating factors (e.g. G-CSF, GM-CSF) and antibiotics -preventive or prophilactic- could be administered according to usual rules in every institution.

Evidence for comparator: -

Actual start date of recruitment	08 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 349
Worldwide total number of subjects	349
EEA total number of subjects	349

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)	243

From 65 to 84 years	106
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	349
Number of subjects completed	349

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

FOLFOX6 modified + bevacizumab

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

Dosage and administration details:

5 mg/Kg IV, day 1 of every cycle (1cycle=2weeks)

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

Dosage and administration details:

85mg/m2 iv administered in 2 hour period, day 1 of cycle

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

Dosage and administration details:

400mg/m2 IV administered in 2 hour period, day 1 of each cycle

Investigational medicinal product name	5-flouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
400 mg/m2 followed by 2400 mg/m2 administered during 48 hours given as continuous infusion.

Arm title	Arm B
Arm description: FOLFOXIRI + bevacizumab	
Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 5 mg/Kg iv day 1 of each cycle (1 cycle= 2weeks)	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 165 mg/m2 IV administered in a 30-90 minutes, day 1 of each cycle	
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 85mg/m2 IV administered in a 2 hour period day 1 of each cycle	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 IV administered in a 2 hour period day 1 of each cycle	
Investigational medicinal product name	5-fluouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 3200 mg/m2 given as continuous infusion during 48 hours, day 1 of each cycle	

Number of subjects in period 1	Arm A	Arm B
Started	177	172
Completed	177	172

Period 2	
Period 2 title	RAS mutated
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Ras mutated
Arm description: -	
Arm type	Ras mutated
No investigational medicinal product assigned in this arm	
Arm title	RAS wild type
Arm description: -	
Arm type	RAS wild type
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Ras mutated	RAS wild type
Started	169	180
Completed	169	180

Period 3	
Period 3 title	BRAF mutated
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes

Arm title	BRAF mutated
Arm description: -	
Arm type	BRAF mutated
No investigational medicinal product assigned in this arm	
Arm title	BRAF wild type
Arm description: -	
Arm type	BRAF wild type
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	BRAF mutated	BRAF wild type
Started	33	316
Completed	33	316

Period 4	
Period 4 title	PI3K mutated
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	PI3K mutated
Arm description: -	
Arm type	PI3K mutated
No investigational medicinal product assigned in this arm	
Arm title	PI3K wild type
Arm description: -	
Arm type	PI3K wild type
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	PI3K mutated	PI3K wild type
Started	43	306
Completed	43	306

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: FOLFOX6 modified + bevacizumab	
Reporting group title	Arm B
Reporting group description: FOLFOXIRI + bevacizumab	

Reporting group values	Arm A	Arm B	Total
Number of subjects	177	172	349
Age categorical Units: Subjects			
Adults (18-64 years)	126	117	243
From 65-84 years	51	55	106
Age continuous Units: years			
arithmetic mean	57.87	59.47	
standard deviation	± 8.43	± 7.72	-
Gender categorical Units: Subjects			
Female	58	54	112
Male	119	118	237
ECOG at baseline Units: Subjects			
ECOG 0	85	81	166
ECOG 1	92	91	183
Tumor location Units: Subjects			
Right	39	48	87
Left	137	119	256
Right and left	1	5	6
Histopathological grade Units: Subjects			
Unknown	38	49	87
Gx: not evaluable	1	2	3
G1: well-differentiated	49	32	81
G2: moderately differentiated	64	72	136
G3: poorly differentiated	22	16	38
G4: undifferentiated	3	1	4
Sincronic or metacronic Units: Subjects			
Sincronic	167	160	327
Metacronic	10	12	22
CEA grouped Units: Subjects			
CEA<=5	8	16	24
CEA>5	169	156	325

Basal surgery Units: Subjects			
NO	118	110	228
Yes (primary tumor)	55	59	114
Yes (not primary tumor)	4	3	7
Previous antineoplastic treatments Units: Subjects			
NO	170	163	333
Yes (adjuvant)	4	7	11
Yes (neoadjuvant)	2	0	2
Yes (neoadjuvant and adjuvant)	1	2	3
Previous radiotherapy Units: Subjects			
No	173	167	340
Yes (adjuvant)	3	4	7
Yes (antialgic)	0	1	1
Yes (neoadjuvant)	1	0	1
RAS (mutational status) Units: Subjects			
Mutated	84	85	169
Native	88	85	173
Unknown	5	2	7
BRAF (mutational status) Units: Subjects			
Mutated	17	16	33
Native	160	156	316
PI3K Units: Subjects			
Mutated	17	26	43
Native	159	146	305
Unknown	1	0	1
Microsatellite instability (MSI) Units: Subjects			
MSI-High	1	2	3
MSI-Low	7	8	15
MSS (microsatellite stable)	156	156	312
Unknown	13	6	19
CEA Units: ng/ml			
arithmetic mean	1537.16	1283.31	
standard deviation	± 4567.79	± 3753.41	-

End points

End points reporting groups	
Reporting group title	Arm A
Reporting group description: FOLFOX6 modified + bevacizumab	
Reporting group title	Arm B
Reporting group description: FOLFOXIRI + bevacizumab	
Reporting group title	Ras mutated
Reporting group description: -	
Reporting group title	RAS wild type
Reporting group description: -	
Reporting group title	BRAF mutated
Reporting group description: -	
Reporting group title	BRAF wild type
Reporting group description: -	
Reporting group title	PI3K mutated
Reporting group description: -	
Reporting group title	PI3K wild type
Reporting group description: -	

Primary: Progression free survival	
End point title	Progression free survival
End point description: Time elapsed from randomization to disease progression or death from any cause.	
End point type	Primary
End point timeframe: Overall study	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	172		
Units: Months				
median (confidence interval 95%)	9.3 (8.5 to 10.7)	12.4 (11.1 to 14.0)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Arm A v Arm B

Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0006
Method	Logrank

Secondary: Overall survival

End point title	Overall survival

End point description:

Time elapsed from randomization to death from any cause.

End point type	Secondary

End point timeframe:

Overall study

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	172		
Units: Months				
median (confidence interval 95%)	17.6 (15.1 to 21.2)	22.3 (17.8 to 26.4)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2627
Method	Logrank

Secondary: Overall response rate

End point title	Overall response rate

End point description:

Percentage of patients with Complete Response or Partial Response

End point type	Secondary

End point timeframe:

Overall study

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	172		
Units: Subjects	92	102		

Statistical analyses

Statistical analysis title	Overall response rate
Statistical analysis description: Overall trial	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1685
Method	Chi-squared
Parameter estimate	Risk difference (RD)

Secondary: Tumor resection rate (R0)

End point title	Tumor resection rate (R0)
End point description: Percentage of patients who achieved complete resection	
End point type	Secondary
End point timeframe: Overall study	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	172		
Units: Subjects				
No	163	160		
Si	14	12		

Statistical analyses

Statistical analysis title	Chi squared test
Comparison groups	Arm A v Arm B

Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.74
Method	Chi-squared
Parameter estimate	Risk difference (RD)

Secondary: Number of patients with grade >=3 treatment-related TEAEs in each arm according to CTCAE v4.0 criteria

End point title	Number of patients with grade >=3 treatment-related TEAEs in each arm according to CTCAE v4.0 criteria

End point description:

Number of patients with grade >=3 treatment-related TEAEs in each arm according to CTCAE v4.0 criteria

End point type	Secondary

End point timeframe:

Overall study

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	170[1]		
Units: Subjects				
YES	119	133		
NO	58	37		

Notes:

[1] - 2 patients don't be evaluated in Safety population because they haven't received any study treatment

Statistical analyses

Statistical analysis title	Chi-squared test
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0216
Method	Chi-squared
Parameter estimate	Risk difference (RD)

Secondary: Number of patients with treatment-related serious TEAEs in each arm according to CTCAE v4.0 criteria

End point title	Number of patients with treatment-related serious TEAEs in each arm according to CTCAE v4.0 criteria

End point description:

Number of patients with treatment-related serious TEAEs in each arm according to CTCAE v4.0 criteria

End point type	Secondary
End point timeframe:	
Overall study	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	170[2]		
Units: Subjects				
Yes	38	60		
No	139	110		

Notes:

[2] - 2 patients weren't considered safety population because they didn't received any study treatment

Statistical analyses

Statistical analysis title	Chi squared test
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0042
Method	Chi-squared
Parameter estimate	Risk difference (RD)

Secondary: Progression free survival according to basal count of circulating tumor cells<=20 /7.5 mL blood

End point title	Progression free survival according to basal count of circulating tumor cells<=20 /7.5 mL blood
End point description:	
Progression free survival according to basal count of circulating tumor cells<=20 /7.5 mL blood	
End point type	Secondary
End point timeframe:	
Overall study	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	152		
Units: Months				
median (confidence interval 95%)	10 (8.9 to 11.1)	12.5 (11.2 to 14.3)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0086
Method	Regression, Cox
Parameter estimate	Log risk ratio

Secondary: Progression free survival according to RAS status	
End point title	Progression free survival according to RAS status
End point description: Progression free survival according to RAS status	
End point type	Secondary
End point timeframe: Overall study	

End point values	Ras mutated	RAS wild type		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	180		
Units: months				
median (confidence interval 95%)	9.1 (8.3 to 11.0)	11.4 (10.5 to 13.6)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Ras mutated v RAS wild type
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0003
Method	Logrank

Secondary: Progression free survival according to BRAF	
End point title	Progression free survival according to BRAF
End point description: Progression free survival according to BRAF	
End point type	Secondary

End point timeframe:
Overall study

End point values	BRAF mutated	BRAF wild type		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	316		
Units: Months				
median (confidence interval 95%)	7.7 (3.7 to 10.6)	11.0 (9.9 to 11.7)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	BRAF mutated v BRAF wild type
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0006
Method	Logrank

Secondary: Progression free survival according to PI3K status

End point title	Progression free survival according to PI3K status

End point description:
Progression free survival according to PI3K status

End point type	Secondary

End point timeframe:
Overall study

End point values	PI3K mutated	PI3K wild type		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	306		
Units: Months				
median (confidence interval 95%)	9.1 (8.1 to 14.2)	10.9 (9.5 to 11.4)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	PI3K mutated v PI3K wild type
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4689
Method	Logrank

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall trial	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B
Reporting group description: -	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 177 (36.16%)	83 / 170 (48.82%)	
number of deaths (all causes)	149	136	
number of deaths resulting from adverse events	13	14	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 177 (1.13%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 177 (1.13%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypovolaemic shock			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
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			
Pyrexia			
subjects affected / exposed	8 / 177 (4.52%)	4 / 170 (2.35%)	
occurrences causally related to treatment / all	3 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse reaction to drug			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General malaise			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
device related pain			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physical condition impairment			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Asthenia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 177 (2.26%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory insufficiency			
subjects affected / exposed	2 / 177 (1.13%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Insterstitial pulmonary disease			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Dissociative disorder			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device thrombosis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
´device dysfunction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (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			
Anastomotic dehiscence			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedure haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical pneumonitis			

subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Pre-syncope			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic-clonic seizures			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (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			
Febrile neutropenia			
subjects affected / exposed	4 / 177 (2.26%)	15 / 170 (8.82%)	
occurrences causally related to treatment / all	4 / 4	15 / 15	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 177 (0.56%)	9 / 170 (5.29%)	
occurrences causally related to treatment / all	1 / 1	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 177 (1.13%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 177 (2.82%)	14 / 170 (8.24%)	
occurrences causally related to treatment / all	4 / 5	12 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	9 / 177 (5.08%)	4 / 170 (2.35%)	
occurrences causally related to treatment / all	7 / 9	4 / 4	
deaths causally related to treatment / all	3 / 4	3 / 3	
Intestinal obstruction			
subjects affected / exposed	2 / 177 (1.13%)	6 / 170 (3.53%)	
occurrences causally related to treatment / all	0 / 2	2 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	4 / 177 (2.26%)	8 / 170 (4.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 3	0 / 7	
Abdominal pain			
subjects affected / exposed	4 / 177 (2.26%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 177 (0.56%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 177 (0.56%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestinal perforation			
subjects affected / exposed	1 / 177 (0.56%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
esophagitis			

subjects affected / exposed	1 / 177 (0.56%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 177 (0.56%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 177 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hipomotility			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			

subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal inflammation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute cholecystitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic insufficiency			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 177 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 177 (1.13%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 177 (1.13%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 177 (0.56%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 177 (0.56%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Anal abscess			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter infection			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diverticulitis			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Respiratory tract infection			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia per Escherichia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal Candidiasis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumococcal pneumonia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Listeriosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Herpesvirus simple encephalitis			

subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal sepsis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphilococcal sepsis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
incision place abscess			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pseudomonas infection urinary tract			

subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 177 (0.00%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lysis tumor syndrome			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	177 / 177 (100.00%)	170 / 170 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	29 / 177 (16.38%)	34 / 170 (20.00%)	
occurrences (all)	29	34	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	119 / 177 (67.23%)	127 / 170 (74.71%)	
occurrences (all)	119	127	
Mucosal inflammation			
subjects affected / exposed	63 / 177 (35.59%)	83 / 170 (48.82%)	
occurrences (all)	63	83	
Pyrexia			
subjects affected / exposed	50 / 177 (28.25%)	54 / 170 (31.76%)	
occurrences (all)	50	54	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	50 / 177 (28.25%)	37 / 170 (21.76%)	
occurrences (all)	50	37	
Cough			
subjects affected / exposed	14 / 177 (7.91%)	16 / 170 (9.41%)	
occurrences (all)	14	16	
Catarrh			
subjects affected / exposed	15 / 177 (8.47%)	14 / 170 (8.24%)	
occurrences (all)	15	14	
Rhinorrhoea			
subjects affected / exposed	9 / 177 (5.08%)	13 / 170 (7.65%)	
occurrences (all)	9	13	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 177 (4.52%)	15 / 170 (8.82%)	
occurrences (all)	8	15	
Investigations			
Decreased weight			
subjects affected / exposed	8 / 177 (4.52%)	10 / 170 (5.88%)	
occurrences (all)	8	10	
Nervous system disorders			
Neurotoxicity			
subjects affected / exposed	71 / 177 (40.11%)	54 / 170 (31.76%)	
occurrences (all)	71	54	
Peripheral neuropathy			

subjects affected / exposed	53 / 177 (29.94%)	41 / 170 (24.12%)	
occurrences (all)	53	41	
Paresthesia			
subjects affected / exposed	53 / 177 (29.94%)	40 / 170 (23.53%)	
occurrences (all)	53	40	
Dysaesthesia			
subjects affected / exposed	27 / 177 (15.25%)	34 / 170 (20.00%)	
occurrences (all)	27	34	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	88 / 177 (49.72%)	104 / 170 (61.18%)	
occurrences (all)	88	104	
Thrombocytopenia			
subjects affected / exposed	60 / 177 (33.90%)	51 / 170 (30.00%)	
occurrences (all)	60	51	
Anemia			
subjects affected / exposed	41 / 177 (23.16%)	45 / 170 (26.47%)	
occurrences (all)	41	45	
Leukopenia			
subjects affected / exposed	10 / 177 (5.65%)	13 / 170 (7.65%)	
occurrences (all)	10	13	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	83 / 177 (46.89%)	130 / 170 (76.47%)	
occurrences (all)	83	130	
Nausea			
subjects affected / exposed	65 / 177 (36.72%)	89 / 170 (52.35%)	
occurrences (all)	65	89	
Vomiting			
subjects affected / exposed	41 / 177 (23.16%)	79 / 170 (46.47%)	
occurrences (all)	41	79	
Constipation			
subjects affected / exposed	47 / 177 (26.55%)	50 / 170 (29.41%)	
occurrences (all)	47	50	
Dysgeusia			

subjects affected / exposed	22 / 177 (12.43%)	30 / 170 (17.65%)	
occurrences (all)	22	30	
Rectal haemorrhage			
subjects affected / exposed	13 / 177 (7.34%)	23 / 170 (13.53%)	
occurrences (all)	13	23	
Upper abdomen pain			
subjects affected / exposed	13 / 177 (7.34%)	20 / 170 (11.76%)	
occurrences (all)	13	20	
Stomatitis			
subjects affected / exposed	8 / 177 (4.52%)	16 / 170 (9.41%)	
occurrences (all)	8	16	
Dry mouth			
subjects affected / exposed	10 / 177 (5.65%)	10 / 170 (5.88%)	
occurrences (all)	10	10	
Proctalgia			
subjects affected / exposed	6 / 177 (3.39%)	13 / 170 (7.65%)	
occurrences (all)	6	13	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 177 (7.34%)	32 / 170 (18.82%)	
occurrences (all)	13	32	
Palmoplantar Erythrodysesthesia Syndrome			
subjects affected / exposed	13 / 177 (7.34%)	8 / 170 (4.71%)	
occurrences (all)	13	8	
Eruption			
subjects affected / exposed	9 / 177 (5.08%)	10 / 170 (5.88%)	
occurrences (all)	9	10	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	10 / 177 (5.65%)	12 / 170 (7.06%)	
occurrences (all)	10	12	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	20 / 177 (11.30%)	14 / 170 (8.24%)	
occurrences (all)	20	14	
Myalgia			

subjects affected / exposed	12 / 177 (6.78%)	11 / 170 (6.47%)	
occurrences (all)	12	11	
Arthralgia			
subjects affected / exposed	10 / 177 (5.65%)	12 / 170 (7.06%)	
occurrences (all)	10	12	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	14 / 177 (7.91%)	9 / 170 (5.29%)	
occurrences (all)	14	9	
Urinary tract infection			
subjects affected / exposed	13 / 177 (7.34%)	9 / 170 (5.29%)	
occurrences (all)	13	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	44 / 177 (24.86%)	56 / 170 (32.94%)	
occurrences (all)	44	56	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2012	Expansion of 14 sites
04 October 2012	Change of PI in Son Llátzer Hospital
01 November 2012	Change PI in Son Espases Hospital
01 February 2013	Change PI in Puerta del Hierro Hospital
10 May 2013	Substantial change to the protocol (Version 4 Protocol- 10May2013- is generated), expansion of 5 sites, change PI in 12 de Octubre Hospital, change in the general Subject Information Sheet
18 March 2014	Substantial change to Protocol (Version 5-18Mar2014) is generated with adition of sub-study and Subject Sheet Information-Informed Consent for sub-study), expansion of 1 site, change of Subject Sheet Information-Informed Consent for study
01 April 2015	Change PI in Virgen del Rocío Hospital
01 October 2015	Change PI in A Coruña Hospital
26 July 2016	Modifications in annexes 8 and 10. Change in Subject Information Sheet-Informed Consent general and specific for sub-study, cahange of 2 responsibles of laboratory of the study, addition of new central laboratory
04 August 2017	Change of PI in 3 sites: Hospital of Valencia, Hospital of Elda, Hospital of Sagunto
12 April 2018	Change of PI in Central University Hospital of Asturias
27 November 2018	Change PI in Hospital of Zamora, change of laboratory of analysis of sub-study
10 July 2019	Substantial change to Protocol (Version 6-10Jul2019) is generated to extent follow up 12 more months

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported