Clinical trial results:
Phase II study of Regorafenib as single agent for the treatment of patients with metastatic colorectal cancer (mCRC) with any RAS or BRAF mutation previously treated with FOLFOXIRI plus bevacizumab.

Summary

EudraCT number	2014-000703-26
Trial protocol	ES
Global end of trial date	24 May 2016

Results information

Result version number	v1 (current)
This version publication date	16 July 2020
First version publication date	16 July 2020

Trial information

Trial identification

Sponsor protocol code	TTD-14-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02175654
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GRUPO DE TRATAMIENTO DE TUMORES DIGESTIVOS (TTD)
Sponsor organisation address	PLAZA DE CASTILLA 3, PTA 8, MADRID, Spain, 28023
Public contact	TTD group, TTD, +34 91378 82 75, ttd@ttdgroup.org
Scientific contact	TTD group, TTD, +34 91378 82 75, 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	20 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 May 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

-To assess the efficacy of single-agent regorafenib in the second-line treatment in metastatic colorectal cancer with any RAS or BRAF mutation previously treated with FOLFOXIRI plus bevacizumab in terms of progression-free survival at 6 months.

Protection of trial subjects:

While on trial, teh patients´best interest was always tried to be ensured, but no specific protection measures were adopted.

Background therapy:

Currently, the first-line treatment strategy established for patients with metastatic colorectal cancer without mutations in RAS (native RAS) is based on the administration of a biological drug (anti-EGFR or an antiangiogenic), in combination with a chemotherapy regimen based on fluoropyrimidines and oxaliplatin or irinotecan. The therapeutic options after the failure of this strategy depend on the treatment used in the first-line environment, therefore oxaliplatin-based regimens are used in patients who have received chemotherapy based on irinotecan in the first line and regimens based on irinotecan in those who have received oxaliplatin in the first line.
This treatment strategy, however, is limited in patients with mutated RAS tumors because they are not eligible for anti-EGFR treatment.

Evidence for comparator:

The concomitant treatment of three of the most active chemotherapeutic agents in mCRC (5-FU, oxaliplatin and irinotecan) in combination with bevacizumab has shown high activity and efficacy as a first-line treatment in patients with mCRC, with manageable toxicity. However, there is no scientific evidence about the best treatment option for patients with mCRC and mutations in RAS or BRAF who have failed a first-line treatment with FOLFOXIRI plus bevacizumab.

Actual start date of recruitment	12 September 2014
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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	9
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

- Recruitment dates: 12/09/14 to 27/11/15.
- A total of 15 patients were recruited in 10 Spanish hospitals.

Pre-assignment

Screening details:

- Eligibility criteria: Patients with metastatic colon/rectum adenocarcinoma with mutations in any gen RAS or BRAF, who have had progression disease after a firstt line treatment with FOLFOXIRI, have measurable disease according to RECIST 1.1, an ECOG 0-1, adequate bone narrow, kidney and liver function and had not recieved regorafenib.

Period 1

Period 1 title	OVERALL TRIAL (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This trial was not blinded.

Arms

Arm title	TREATMENT OVEALL POPULATION

Arm description:

Regorafenib at the initial dose of 160 mg dadily, 3 weeks on and one off, with cycles of 28 days. Treatment will maintained until progressive disease, unacceptable toxicity, withdrawal of the consent or investigator´s decision.

Arm type	Experimental
Investigational medicinal product name	REGORAFENIB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Regorafenib was administres at an initial dose o 160 mg/day, three weeks on and one week off.

Number of subjects in period 1	TREATMENT OVEALL POPULATION
Started	15
Completed	15

Baseline characteristics

Reporting groups

Reporting group title	OVERALL TRIAL

Reporting group description: -

Reporting group values	OVERALL TRIAL	Total	
Number of subjects	15	15	
Age categorical 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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
From 18 years	15	15	
Age continuous Units: years			
arithmetic mean	64.73		
standard deviation	± 8.81	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	13	13	
KRAS STATUS Units: Subjects			
KRAS MUTATED	9	9	
KRAS WILD-TYPE	6	6	
KRAS ND	0	0	
BRAF STATUS Units: Subjects			
BRAF MUTATED	2	2	
BRAF WILD-TYPE	12	12	
BRAF ND	1	1	
NRAS STATUS Units: Subjects			
NRAS MUTATED	3	3	
NRAS WILD-TYPE	3	3	
NRAS ND	9	9	
RAS STATUS			
RAS status considering both genes, KRAS and NRAS			
Units: Subjects			
RAS MUTATED	12	12	

RAS WILD-TYPE	2	2	
RAS ND	1	1	

Subject analysis sets

Subject analysis set title	INTENT-TO-TREAT POPULAITON
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT- populations includes all those patients who were enrolled in the trial and recieved, at least, one dose of the study drug.

Reporting group values	INTENT-TO-TREAT POPULAITON		
Number of subjects	15		
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		
From 18 years	15		
Age continuous Units: years			
arithmetic mean	64.73		
standard deviation	± 8.81		
Gender categorical Units: Subjects			
Female	2		
Male	13		
KRAS STATUS Units: Subjects			
KRAS MUTATED	9		
KRAS WILD-TYPE	6		
KRAS ND	0		
BRAF STATUS Units: Subjects			
BRAF MUTATED	2		
BRAF WILD-TYPE	12		
BRAF ND	1		
NRAS STATUS Units: Subjects			
NRAS MUTATED			
NRAS WILD-TYPE			
NRAS ND			
RAS STATUS			

RAS status considering both genes, KRAS and NRAS			
Units: Subjects			
RAS MUTATED	12		
RAS WILD-TYPE	2		
RAS ND	1		

End points

End points reporting groups

Reporting group title	TREATMENT OVEALL POPULATION
Reporting group description:	
Regorafenib at the initial dose of 160 mg dadily, 3 weeks on and one off, with cycles of 28 days. Treatment will maintained until progressive disease, unacceptable toxicity, withdrawal of the consent or investigator´s decision.	
Subject analysis set title	INTENT-TO-TREAT POPULAITON
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT- populations includes all those patients who were enrolled in the trial and recieved, at least, one dose of the study drug.	

Primary: PFS at 6 months of study entry

End point title	PFS at 6 months of study entry
End point description:	
PFS at 6 months of study entry	
End point type	Primary
End point timeframe:	
Overall trial	

End point values	TREATMENT OVEALL POPULATION	INTENT-TO-TREAT POPULAITON		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: Percentage	0	0		

Statistical analyses

Statistical analysis title	PFS at 6 months of study entry
Comparison groups	TREATMENT OVEALL POPULATION v INTENT-TO-TREAT POPULAITON
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	CI estimation

Secondary: PROGRESSION-FREE SURVIVAL (PFS)

End point title	PROGRESSION-FREE SURVIVAL (PFS)
End point description:	

End point type	Secondary

End point timeframe:

Defined as time from the study entry to first radiographic progression disease or death. Those patients not fulfilling these creteria were censored at the time of the last evaluable visit of the patient.

End point values	TREATMENT OVEALL POPULATION	INTENT-TO-TREAT POPULAITON		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	15		
Units: Months				
median (confidence interval 95%)	2.24 (1.18 to 2.70)	2.24 (1.18 to 2.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: TIME TO PROGRESSION

End point title	TIME TO PROGRESSION

End point description:

End point type	Secondary

End point timeframe:

Time from study entry to the date of the first progression disease or death. Those patients not fulfilling these criteria were censored at the time of the last evaluable visit.

End point values	INTENT-TO-TREAT POPULAITON			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	2.01 (1.18 to 2.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: TIME TO TREATMENT FAILURE

End point title	TIME TO TREATMENT FAILURE

End point description:

End point type	Secondary

End point timeframe:

Time from study entry to the end date of treatment, whatever the reason was.

End point values	INTENT-TO-TREAT POPULAITON			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	2.27 (1.25 to 2.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: OVERALL SURVIVAL

End point title	OVERALL SURVIVAL

End point description:

End point type	Secondary

End point timeframe:

Time from the study entry to the date of death by any cause.

End point values	INTENT-TO-TREAT POPULAITON			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	3.35 (1.94 to 4.37)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were registered from the time of the ICF signature to 28 days after the last dose of the study frug.

Adverse event reporting additional description:

Each event was described in detail along with the start and end dates, the intensity, the relationship with the product under investigation, the measures taken and the outcome.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4.0

Reporting groups

Reporting group title	OVERALL POPULATION

Reporting group description:

The adverse events will be described in the overall population of this study because the overall population recieved at least one dose of treatment and represent the safety population.

Serious adverse events	OVERALL POPULATION		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PROGRESSION DISEASE			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
THORACIC PAIN			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
DIARRHEA			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
ABDOMINAL PAIN			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
INTESTINAL BLEEDING			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Hepatobiliary disorders			
HEPATIC INSUFICIENCY			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Infections and infestations			

INFECTION OF THE CATHETER SITE			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.01 %

Non-serious adverse events	OVERALL POPULATION		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Disease progression			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	10 / 15 (66.67%)		
occurrences (all)	10		
Proctalgia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Physical disability			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
THORACIC PAIN			

subjects affected / exposed occurrences (all) THORACIC NOT CARDIAC PAIN subjects affected / exposed occurrences (all) Sudden death subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Respiratory, thoracic and mediastinal disorders Dysphonia subjects affected / exposed occurrences (all) Hippus subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Respiratory disorder subjects affected / exposed occurrences (all) Aphonia subjects affected / exposed occurrences (all)	 5 / 15 (33.33%) 5 2 / 15 (13.33%) 2 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 2 / 15 (13.33%) 2 1 / 15 (6.67%) 1		
Investigations			

BILIRUBIN INCREASED			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
ALCALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Ear and labyrinth disorders ACUPHENES subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1		
Eye disorders Eye irritation subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Atrophic glossitis subjects affected / exposed occurrences (all) Gastrointestinal haemorrhage	 9 / 15 (60.00%) 9 8 / 15 (53.33%) 8 3 / 15 (20.00%) 3 3 / 15 (20.00%) 3 3 / 15 (20.00%) 3 3 / 15 (20.00%) 3 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Anal inflammation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Odynophagia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Intestinal perforation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Proctalgia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
ERUPTION			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pigmentation disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
EXTREMITY PAIN			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Catheter site infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2015	CHANGE IP
01 February 2016	PREMATURE END OF STUDY BECAUSE OF LOW RECRUITMENT

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 February 2016	PREMATURE END OF STUDY BECAUSE OF LOW RECRUITMENT	-

Notes:

Limitations and caveats

None reported