Clinical trial results:
Phase II study of Regorafenib as a single agent for first-line treatment of patients with metastatic colorectal cancer (MCRC) who are fragile and/or not candidates for polychemotherapy

Summary

EudraCT number	2013-000236-94
Trial protocol	ES
Global end of trial date	04 April 2016

Results information

Result version number	v1 (current)
This version publication date	22 July 2020
First version publication date	22 July 2020

Trial information

Trial identification

Sponsor protocol code	TTD-13-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01875380
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo de Tratamiento de los Tumores Digestivos (TTD)
Sponsor organisation address	Téllez nº30 posterior, planta 1ª, oficina 4-2/4-3, Madrid, Spain, 28007
Public contact	TTD, Grupo de Tratamiento de los Tumores Digestivos (TTD), +34 913788275, ttd@ttdgroup.org
Scientific contact	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	22 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2016
Global end of trial reached?	Yes
Global end of trial date	04 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of single-agent regorafenib in terms of progression-free survival at 6 months.

Protection of trial subjects:

All patients have been treated according to GCP criteria.
Patients were entitled to withdraw from the study at any time and for any reason without prejudice of their future medical care on the part of the doctor or the center.
Doses of regorafenib could be reduced/delayed in case of adverse events (AEs) as per protocol.
Any medication that patients needed for their correct clinical control (except prohibited therapies), according to investigator's criteria were allowed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2013
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: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

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)	3
From 65 to 84 years	40
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Patients were included in the study between June 25, 2013 and February 9, 2015.

Pre-assignment

Screening details:

Informed consent, criteria of fragility, ECG, CT of the thorax, abdomen and pelvis, blood count, biochemistry, proteinuria, coagulation tests.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Regorafenib arm

Arm description:

Regorafenib was administered at an initial dose of 160 mg per day, orally, for 3 weeks followed by 1 week of rest.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY 73-4506
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Regorafenib was administered at an initial dose of 160 mg per day, orally, for 3 weeks followed by 1 week of rest.

Number of subjects in period 1	Regorafenib arm
Started	47
Completed	47

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	47	47	
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)	3	3	
From 65-84 years	40	40	
85 years and over	4	4	
Age continuous Units: years			
median	80.8		
full range (min-max)	63.2 to 89.2	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	26	26	
ECOG Units: Subjects			
ECOG 0	5	5	
ECOG 1	25	25	
ECOG 2	17	17	
UNFIT criteria Units: Subjects			
Dependent	8	8	
Comorbidities	13	13	
Geriatric syndrome	6	6	
Dependent and geriatric syndrome	6	6	
Dependent and comorbidities	8	8	
Comorbidities and geriatric syndrome	2	2	
Dependent, comorbidities and geriatric syndrome	4	4	
Tumor location Units: Subjects			
Colon	32	32	
Rectum	14	14	
Colon and rectum	1	1	

Number of lesions Units: Subjects			
One	4	4	
Two	6	6	
Three	13	13	
Four	6	6	
Five	4	4	
Six	6	6	
Seven	3	3	
Eight	5	5	
Affected sites Units: Subjects			
One	17	17	
Two	14	14	
Three	12	12	
Four	2	2	
Five	2	2	
Administered cycles Units: Subjects			
One	11	11	
Two	14	14	
Three	5	5	
Four	3	3	
Five	1	1	
Six	2	2	
Seven	3	3	
Eight	3	3	
Nine	1	1	
Twelve	2	2	
Seventeen	1	1	
Twenty	1	1	
Number of delayed cycles Units: Subjects			
None	34	34	
One	8	8	
Two	2	2	
Three	1	1	
Four	2	2	
Number of dose reductions Units: Subjects			
None	21	21	
One	16	16	
Two	9	9	
Three	1	1	
Previous surgery Units: Subjects			
Yes	31	31	
No	16	16	
Adjuvant treatment Units: Subjects			
Yes	7	7	

No	40	40	
Previous radiotherapy Units: Subjects			
Yes	6	6	
No	41	41	
Liver metastases Units: Subjects			
Yes	31	31	
No	16	16	
Lung metastases Units: Subjects			
Yes	29	29	
No	18	18	
Weight Units: kilogram(s)			
median	71.5		
full range (min-max)	43.0 to 105.9	-	
Height Units: Centimeter			
median	159		
full range (min-max)	142 to 180	-	
Heart rate Units: Beats per minute			
median	76		
full range (min-max)	59 to 104	-	
Systolic blood pressure Units: Mm Hg			
median	134		
full range (min-max)	104 to 153	-	
Diastolic blood pressure Units: Mm Hg			
median	70		
full range (min-max)	50 to 90	-	
Time from metastatic diagnosis Units: Months			
median	1.6		
full range (min-max)	0.1 to 21.6	-	
Dose intensity Units: percent			
median	76		
full range (min-max)	48 to 101	-	

End points

End points reporting groups

Reporting group title	Regorafenib arm

Reporting group description:

Regorafenib was administered at an initial dose of 160 mg per day, orally, for 3 weeks followed by 1 week of rest.

Primary: 6 months progression free survival

End point title	6 months progression free survival[1]

End point description:

End point type	Primary

End point timeframe:

Every 8 weeks. Progression free survival was defined as the time (in months) between the date of inclusioin and the date of first documented disease progression or death, whichever occurs first.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: One arm non-controlled clinical trial. Only descriptive analyses performed. No comparisons.

End point values	Regorafenib arm			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Probability				
number (confidence interval 95%)	45.0 (29.7 to 60.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

Every 8 weeks. Progression free survival was defined as the time (in months) between the date of inclusioin and the date of first documented disease progression or death, whichever occurs first.

End point values	Regorafenib arm			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: months				
median (confidence interval 95%)	5.6 (2.7 to 8.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response

End point title	Response

End point description:

Tumor evaluation according to RECIST 1.1 criteria

End point type	Secondary

End point timeframe:

Every 8 weeks

End point values	Regorafenib arm			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Patients				
Complete response	1			
Partial response	2			
Stable disease	21			
Progression disease	13			
Not evaluable	10			

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:

Every 8 weeks. Overall survival was defined as the time (in months) between the date of inclusioin and the date of death.

End point values	Regorafenib arm			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Months				
median (confidence interval 95%)	16.0 (7.8 to 24.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate

End point title	Overall response rate
End point description: Complete response + Partial response	
End point type	Secondary
End point timeframe: Every 8 weeks	

End point values	Regorafenib arm			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: percent				
number (confidence interval 95%)	6.4 (0.0 to 13.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate

End point title	Disease control rate
End point description: Complete response + Partial response + Stable disease	
End point type	Secondary
End point timeframe: Every 8 weeks	

End point values	Regorafenib arm			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: percent				
number (confidence interval 95%)	51.1 (36.8 to 65.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of the informed consent until at least 28 days after the last administered dose of the study treatment.

Adverse event reporting additional description:

Grade 3 - 5 adverse events according to NCI-CTC AE version 4.0 have been reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Regorafenib arm

Reporting group description:

Regorafenib was administered at an initial dose of 160 mg per day, orally, for 3 weeks followed by 1 week of rest.

Serious adverse events	Regorafenib arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 47 (46.81%)		
number of deaths (all causes)	26		
number of deaths resulting from adverse events	5		
Investigations			
Lipase increased			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
General physical health deterioration			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mucosal inflammation			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 2		

Constipation			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	5 / 47 (10.64%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 3		
Vomiting			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Abdominal abscess			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Regorafenib arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 47 (100.00%)		
Investigations			
Alanine aminotransferase increased	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		

Aspartate aminotransferase increased	Additional description: Grade 3		
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased	Additional description: Grade 3		
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Lipase increased	Additional description: Grade 3&4		
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Vascular disorders			
Hypertension	Additional description: Grade 3 (14) & Grade 4 (1)		
subjects affected / exposed	15 / 47 (31.91%)		
occurrences (all)	15		
Nervous system disorders			
Cerebrovascular accident	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Aphonia	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Somnolence	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia	Additional description: Grade 3		
subjects affected / exposed	14 / 47 (29.79%)		
occurrences (all)	14		
Mucosal inflammation	Additional description: Grade 3		
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Gastrointestinal disorders			
Dry mouth	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Diarrhoea	Additional description: Grade 3		

subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	4		
Abdominal pain	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Stomatitis	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Constipation	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Rectal haemorrhage	Additional description: Grade 3&5		
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Nausea	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Pancreatitis	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Intestinal perforation	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hyperbilirubinaemia	Additional description: Grade 3		
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dermatitis	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome	Additional description: Grade 3		
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	4		
Renal and urinary disorders			

Proteinuria	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Infections and infestations			
Vulvovaginal inflammation	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Abscess	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Pneumonia	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Grade 3		
subjects affected / exposed	2 / 47 (4.26%)		
occurrences (all)	2		
Hyperglycaemia	Additional description: Grade 3		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Hyperuricaemia	Additional description: Grade 4		
subjects affected / exposed	1 / 47 (2.13%)		
occurrences (all)	1		
Hypophosphataemia	Additional description: Grade 3		
subjects affected / exposed	6 / 47 (12.77%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported