



## 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
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##### 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:

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**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:

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**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:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Spain: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

Notes:

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**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

<b>Arm title</b>	Regorafenib arm
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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.

<b>Number of subjects in period 1</b>	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 full range (min-max)	71.5 43.0 to 105.9	-	
Height Units: Centimeter median full range (min-max)	159 142 to 180	-	
Heart rate Units: Beats per minute median full range (min-max)	76 59 to 104	-	
Systolic blood pressure Units: Mm Hg median full range (min-max)	134 104 to 153	-	
Diastolic blood pressure Units: Mm Hg median full range (min-max)	70 50 to 90	-	
Time from metastatic diagnosis Units: Months median full range (min-max)	1.6 0.1 to 21.6	-	
Dose intensity Units: percent median full range (min-max)	76 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 <sup>[1]</sup>
End point description:	

End point type	Primary
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End point timeframe:

Every 8 weeks. Progression free survival was defined as the time (in months) between the date of inclusion 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.

<b>End point values</b>	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
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End point timeframe:

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

<b>End point values</b>	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	

<b>End point values</b>	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 inclusion 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	

<b>End point values</b>	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

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	Regorafenib arm
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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		
<b>Infections and infestations</b>			
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		
<b>Metabolism and nutrition disorders</b>			
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 %

<b>Non-serious adverse events</b>	Regorafenib arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 47 (100.00%)		
<b>Investigations</b>			
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 erythrodysesthesia syndrome	Additional description: Grade 3		
subjects affected / exposed	4 / 47 (8.51%)		
occurrences (all)	4		
Renal and urinary disorders			



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

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported