Clinical trial results:
A Phase II study of Axitinib as maintenance for patients with advanced colorectal carcinoma.

Summary

EudraCT number	2011-002384-16
Trial protocol	ES
Global end of trial date	30 September 2015

Results information

Result version number	v1 (current)
This version publication date	16 July 2020
First version publication date	16 July 2020
Summary attachment (see zip file)	Friendly description (Friendly description.docx)

Trial information

Trial identification

Sponsor protocol code	TTD-11-01/AXI-IIG-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	TTD
Sponsor organisation address	C/Téllez 30, planta 1ª, oficina 4-2/4-3, Madrid, Spain, 28007
Public contact	Inmaculada Ruiz de Mena, TTD, +34 +34 91 3788275, ttd@ttdgroup.org
Scientific contact	Inmaculada Ruiz de Mena, TTD, +34 +34 91 3788275, 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	17 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2015
Global end of trial reached?	Yes
Global end of trial date	30 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if the maintenance therapy with AG-013736 is able to improve the PFS in patients with low risk of recurrence and advanced CRC without progressive disease after 6 months of treatment with an standard front line chemotherapy

Protection of trial subjects:

Palliative treatment and supportive treatment for symptoms related to the disease, including pain treatments. Patients could receive loperamide and other treatments for diarrhea. Narcotic or anti-inflammatory analgesics could be used if needed. Antibiotics could be used if needed. Epoetin, darbepoetin and Colony Stimulating Factors could be used if needed. Transfusion of red blood cells or platelets could be used if needed. Low dose of oral steroids (short cycle) or topical or inhaled corticosteroids could be used if needed. Antihypertensive therapy (with amlodipine, bepridil, felodipine) if needed.

Background therapy:

Colorectal cancer (CRC) is the third most common type of cancer worldwide and the fourth leading cause of death.
The prognosis of patients with metastatic CRC has improved significantly due to the introduction of effective cytotoxic drugs in first-line therapy (irinotecan and oxaliplatin), which in turn don't present cross-resistance, in combination with targeted agents such as epidermal growth factor inhibitors and vascular endothelial growth factor inhibitors. The median survival of these patients is approximately 2 years, and they are usually treated until progression or unacceptable toxicity; consequently it is needed the evaluation of new treatment alternatives which allow to control tumor progression and minimize all accumulative adverse events, providing a good quality of life to the patients as long as possible.

Evidence for comparator:

Axitinib (AG-013736) is an tyrosine kinase inhibitor that inhibits the proangiogenic cytokines VEGF and PDGF, exerting consequently an antiangiogenic effect. Phase 2 trials are have been completed or are ongoing in several kind of tumors: metastatic breast cancer non small cell lung cancer, renal cell carcinoma, thyroid cancer, malignant melanoma, advanced pancreatic cancer and colorectal cancer. One pivotal phase 3 study in renal cell carcinoma is currently active.
The adverse events reported in clinical trials are considered manageable, usually reversible and expected for this kind of agents. The adverse events more commonly reported were: fatigue, diarrhea, hypertension, anorexia, nausea, dysphonia, Palmoplantar Erythrodysestesia Syndrome, weight loss, headache, cough, constipation, proteinuria and hypothiroidism. Grade 3 adverse events or superior more common occurred were hypertension and fatigue.

Actual start date of recruitment	24 February 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: 49

Worldwide total number of subjects	49
EEA total number of subjects	49

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)	18
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on 24Feb2012 and the last patient was enrolled 06Oct2014. Patients were enrolled in 11 Spanish sites.

Pre-assignment

Screening details:

Patients with metastatic colorectal carcinoma, that had achieved disease control after 6-8 months of first-line chemotherapy and that presented low tumor burden. Randomization was stratified according to ECOG (0 vs 1) and previous treatment with bevacizumab or cetuximab (Yes vs No).

Pre-assignment period milestones

Number of subjects started	49
Intermediate milestone: Number of subjects	Overall trial: 49
Number of subjects completed	49

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Sealed randomization envelopes will be delivered to the investigators so that they can do the unmasking in case that a medical emergency for the patient safety occurs.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Axitinib

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg twice a day

Arm title	Arm B

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
5 mg twice a day

Number of subjects in period 1	Arm A	Arm B
Started	25	24
Completed	25	24

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: Axitinib	
Reporting group title	Arm B
Reporting group description: Placebo	

Reporting group values	Arm A	Arm B	Total
Number of subjects	25	24	49
Age categorical Units: Subjects			
Adults (18-64 years)	8	10	18
Adults (65-84 years)	17	14	31
Age continuous Units: years			
arithmetic mean	66.4	66.04	
inter-quartile range (Q1-Q3)	63 to 74	60 to 72.5	-
Gender categorical Units: Subjects			
Female	9	7	16
Male	16	17	33
ECOG Units: Subjects			
ECOG 0	9	10	19
ECOG 1	16	14	30

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Axitinib	
Reporting group title	Arm B
Reporting group description: Placebo	

Primary: Progression Free Survival in arm A and in arm B

End point title	Progression Free Survival in arm A and in arm B
End point description: Evaluate if maintenance therapy with axitinib improves Progression Free in patients with metastatic colorectal cancer without disease progression after 6 months of treatment with any standard first-line chemotherapy and with low tumor burden in comparison with placebo.	
End point type	Primary
End point timeframe: Time elapsed (in months) since date of randomization of the patient until date of first observed progression or until date of death of any cause (whichever comes first)	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: months				
median (inter-quartile range (Q1-Q3))	4.96 (2.6 to 8.61)	3.16 (1.84 to 5.04)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Model
Statistical analysis description: Time elapsed (in months) between randomization date until date of first progression observed or date of death by any cause (if it happened before progression). In the case that patient hadn't progressed or died, they will be censored in last tumoral evaluation date.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0116 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4642

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2515
upper limit	0.8565
Variability estimate	Standard error of the mean

Notes:

[1] - p value for Long Rank Test

Secondary: Best Overall response rate in arm A and in arm B

End point title	Best Overall response rate in arm A and in arm B

End point description:

Evaluate and compare the Best overall response rate (according to RECIST criteria) to the treatment in patients in arm A and in patients in arm B

End point type	Secondary

End point timeframe:

Best overall response rate (according to RECIST criteria) to the treatment in all evaluations performed in patients in arm A and in patients in arm B

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: Number of patients				
number (not applicable)				
RC	0	0		
RP	1	0		
EE	17	11		
DP	7	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

Time (in months) elapsed since the date of randomization of the patient until the first progression observed (radiological or clinical, whichever comes first). In the case that patient wouldn't progressed they was censored in the last date of tumor evaluation

End point type	Secondary

End point timeframe:

Time (in months) elapsed since the date of randomization of the patient until the first progression observed (radiological or clinical, whichever comes first)

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: months				
median (inter-quartile range (Q1-Q3))	4.96 (2.6 to 8.61)	3.16 (1.84 to 5.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Time (in months) elapsed since date of the beginning of the treatment until date of death by any cause

End point type	Secondary

End point timeframe:

Time (in months) elapsed since date of the beginning of the treatment until date of death by any cause

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: months				
arithmetic mean (inter-quartile range (Q1-Q3))	27.61 (14.96 to 38.94)	19.99 (11.74 to 31.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Number of patients that present as Best Overall Response (in all evaluations performed): Complete Response or Partial Response

End point type	Secondary

End point timeframe:

Number of patients that present as Best Overall Response (in all evaluations performed): Complete Response or Partial Response

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: Number of patients				
number (not applicable)				
CR	0	0		
PR	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Since the moment that patient signed the informed consent until 28 days after the last administration of the study drug	
Adverse event reporting additional description:	
Any untoward medical event that happens in a patient enrolled in a clinical trial	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Patients receiving axitinib	
Reporting group title	Arm B
Reporting group description:	
Patients receiving placebo	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	1 / 24 (4.17%)	
number of deaths (all causes)	11	15	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasia progression			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Injury, poisoning and procedural complications			
Termal burn			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			

subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (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	25 / 25 (100.00%)	22 / 24 (91.67%)	
Vascular disorders			
Arterial hypertension			
subjects affected / exposed	14 / 25 (56.00%)	3 / 24 (12.50%)	
occurrences (all)	14	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 25 (68.00%)	8 / 24 (33.33%)	
occurrences (all)	17	8	
Mucosal inflammation			
subjects affected / exposed	8 / 25 (32.00%)	0 / 24 (0.00%)	
occurrences (all)	8	0	
Pyrexia			

subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Pruritus			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Catarrh			
subjects affected / exposed	1 / 25 (4.00%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Dysphonia			
subjects affected / exposed	3 / 25 (12.00%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Oropharingeal pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	4 / 25 (16.00%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Nervous system disorders			
Aphonia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	5 / 25 (20.00%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	

Neurotoxicity			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
paresthesia			
subjects affected / exposed	3 / 25 (12.00%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 25 (12.00%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 25 (64.00%)	3 / 24 (12.50%)	
occurrences (all)	16	3	
Dyspepsia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	3 / 25 (12.00%)	3 / 24 (12.50%)	
occurrences (all)	3	3	
abdominal superior part pain			
subjects affected / exposed	2 / 25 (8.00%)	3 / 24 (12.50%)	
occurrences (all)	2	3	
Constipation			
subjects affected / exposed	8 / 25 (32.00%)	3 / 24 (12.50%)	
occurrences (all)	8	3	
Rectal haemorrhage			
subjects affected / exposed	4 / 25 (16.00%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Nausea			
subjects affected / exposed	6 / 25 (24.00%)	3 / 24 (12.50%)	
occurrences (all)	6	3	
Vomiting			
subjects affected / exposed	7 / 25 (28.00%)	2 / 24 (8.33%)	
occurrences (all)	7	2	
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
eruption			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Palmoplantar erythrodysesthesia			
subjects affected / exposed	4 / 25 (16.00%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Nail disorder			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	3 / 25 (12.00%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Endocrine disorders			
Hipothyroidism			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 25 (12.00%)	3 / 24 (12.50%)	
occurrences (all)	3	3	
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	3 / 24 (12.50%)	
occurrences (all)	2	3	
Extremity pain			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Muculoskeletal pain			
subjects affected / exposed	3 / 25 (12.00%)	0 / 24 (0.00%)	
occurrences (all)	3	0	

Myalgia subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 24 (0.00%) 0	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	0 / 24 (0.00%) 0	
Metabolism and nutrition disorders Appetite decreased subjects affected / exposed occurrences (all)	13 / 25 (52.00%) 13	5 / 24 (20.83%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2011	A new point is included: Unmasking: Site will be taught in unmasking process. Sealed randomization envelopes will be delivered to the investigator so that they can do the unmasking in case that a medical emergency for the patient safety occurs. The first paragraph in sponsor interruption criteria is modified. Before amendment: This study can be interrupted prematurely by health authorities, changes in CEIC decision or drug safety problems or at the sponsor criteria or Pfizer criteria. Moreover, Pfizer reserves the right to suspend Axitinib development at any time. after amendment: This study can be interrupted prematurely by health authorities, changes in CEIC decision or drug safety problems or at the sponsor criteria
10 April 2012	Changes in study design: Before: patients with disease control after 6 month of first line chemotherapy. Amendment: after 6-8 months. Before: patients with < 50% of liver affected. Amendment: patients with < 50% of liver affected and/or <15% of lungs affected. Before: period between the end of previous treatment for colorectal cancer (CRC) and beginning of study treatment will be 4 weeks. Amendment: period between the end of previous treatment for colorectal cancer (CRC) and beginning of study treatment will be 4 -6 weeks. Change in inclusion criteria 6: Before: serum creatinine< or = 1.5 ULN or creatinine clearance calculated> or=50 mL/min. Amendment: serum creatinine< or = 1.5 ULN and creatinine clearance calculated> or=50 mL/min. INR<1.5. Addition in general circumstances for study treatment delay: systolic blood pressure<150 and diastolic blood pressure<100 mmHg.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported