Clinical trial results:
Phase II study of panitumumab as a first line agent in fragile elderly patients with advanced colorectal cancer with non-mutated KRAS

Summary

EudraCT number	2009-016661-28
Trial protocol	ES
Global end of trial date	31 July 2014

Results information

Result version number	v1 (current)
This version publication date	27 March 2019
First version publication date	27 March 2019

Trial information

Trial identification

Sponsor protocol code	TTD-09-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01126112
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)
Sponsor organisation address	C/ Téllez nº30 posterior, planta 1ª, oficina 4-2/4-3, Madrid, Spain, 28007
Public contact	Inmaculada Ruiz de Mena, Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD), +34 913788275, ttd@ttdgroup.org
Scientific contact	Inmaculada Ruiz de Mena, Spanish Cooperative Group for the Treatment of Digestive Tumors (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	31 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 September 2013
Global end of trial reached?	Yes
Global end of trial date	31 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the 6-month progression-free survival (PFS) of frail elderly subjects treated with panitumumab as a first-line chemotherapy regimen in subjects with metastatic colorectal cancer (mCRC) with non-mutated KRAS.

Protection of trial subjects:

Throughout the study, the researchers were able to prescribe any medication or concomitant treatment they considered necessary to provide adequate supportive assistance. Topical, oral or intravenous antibiotics were used to treat skin or nail-related toxicities at the discretion of the investigator. For the subjects with anticoagulant treatment, a strict control of the coagulation parameters was recommended during the treatment period of the study. For low white blood cell count, granulocyte colony stimulating factor (G-CSF) could be used; however in this trial the routine prophylactic use of G-CSF was not recommended. G-CSF for therapeutic purposes in patients with serious neutropenic complications such as tissue infections, sepsis, fungal infections, etc., could be administered at the discretion of the investigator or if it was the standard protocol in the institution. Regional variations were acceptable practice. The epoetins could be used according to the investigator's criteria to treat chemotherapy-induced anemia.

Background therapy:

It is widely known that frail elderly patients with mCRC are not candidates for chemotherapy due to potential undesirable effects, including the possibility of toxic death, which exceeds the potential benefits in quality of life and survival. The anti-epidermal growth factor receptor (EGFR) monoclonal antibody, Panitumumab, has demonstrated efficacy and a manageable safety profile as a monotherapy and in combination with chemotherapy (as first- or second-line therapy), for the treatment of mCRC in patients with wild-type (WT) KRAS (exon 2) tumours. In addition, the toxicity profile is moderate when used in monotherapy; the main toxicity occurs in the skin. Finally, because of its pharmacokinetic profile, panitumumab can be administered every 2 weeks, which reduces hospital visits compared to the weekly schedule. Studies of the factors that predict efficacy have shown that patients with non-mutated KRAS can only benefit from an anti-EGFR treatment.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	21 July 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	0
From 65 to 84 years	28
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

33 patients were included: 22 males and 11 females. All patients were Caucasians. This was a national study with all patients being included at 14 Spanish sites.

Pre-assignment

Screening details:

Key inclusion criteria: patients ≥70 years of age; patients with mCRC not prone for surgical resection; WT KRAS (exon 2); measurable disease according to the mRECIST criteria (version 1.1); ECOG status 6 3; magnesium levels ≥ the lower limit of normal. Intermediate or high risk prognostic factors according to KPC ineligible for chemotherapy.

Pre-assignment period milestones

Number of subjects started	33
Number of subjects completed	33

Period 1

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

Arms

Arm title	Wild-type KRAS mCRC

Arm description:

Wild-type KRAS mCRC patients. Panitumumab will be administered by intravenous (i.v.) infusion at a dose of 6 mg/kg once every 14 days until disease progression is diagnosed, at which time those subjects will be withdrawn from the treatment phase.

Arm type	Experimental
Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	Vectibix
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered every 14 days at a dose of 6 mg/kg, over a 30–90 (±15) minute intravenous infusion.

Number of subjects in period 1	Wild-type KRAS mCRC
Started	33
Completed	33

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
Frail elderly patients with wilD-type KRAS mCRC and poor prognostic factors (intermediate- or high-risk according to the KPC) received panitumumab until progression or unavveptable toxicity.	

Reporting group values	Baseline	Total	
Number of subjects	33	33	
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	5	5	
Adults (70-85 years)	28	28	
Age continuous Units: years			
median	81		
full range (min-max)	73 to 89	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	22	22	

End points

End points reporting groups

Reporting group title	Wild-type KRAS mCRC

Reporting group description:

Wild-type KRAS mCRC patients. Panitumumab will be administered by intravenous (i.v.) infusion at a dose of 6 mg/kg once every 14 days until disease progression is diagnosed, at which time those subjects will be withdrawn from the treatment phase.

Subject analysis set title	Mutant RAS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with mutant RAS

Subject analysis set title	Wild-type RAS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with wild-type RAS

Primary: Progression free survival (at 6 months)

End point title	Progression free survival (at 6 months)[1]

End point description:

End point type	Primary

End point timeframe:

Is defined as the percentage of subjects living free of disease progression, as defined in the RECIST version 1.1 criteria, 6 months after inclusion in the study.

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: No statistical analysis was planned for this primary outcome measure.

End point values	Wild-type KRAS mCRC			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percent				
number (confidence interval 95%)	36.4 (20.0 to 52.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

The ORR will be estimated for confirmed values and the bilateral 95% confidence limits will be presented. Additionally, the influence of the covariables of interest (7.8 Adjustments for covariables) will be explored through a logistic regression model.

End point type	Secondary

End point timeframe:

The ORR (incidence of complete response or partial response) confirmed radiologically during the treatment period.

End point values	Wild-type KRAS mCRC			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percent				
number (confidence interval 95%)	9.1 (0.0 to 18.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

End point type	Secondary

End point timeframe:

The OS time is defined as the number of days elapsed from the date of inclusion in the study until the date of death.

End point values	Wild-type KRAS mCRC			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: months				
median (confidence interval 95%)	7.1 (5.0 to 12.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

End point type	Secondary

End point timeframe:

The DCR will be defined as the time from inclusion until the date of confirmation of objective response, calculated for the subjects with an objective response.

End point values	Wild-type KRAS mCRC			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: percent				
number (confidence interval 95%)	63.6 (47.2 to 80.1)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Progression free survival (RAS status)

End point title	Progression free survival (RAS status)

End point description:

End point type	Post-hoc

End point timeframe:

At the end of follow-up.

End point values	Mutant RAS	Wild-type RAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	15		
Units: Months				
median (confidence interval 95%)	2.8 (1.4 to 4.5)	7.9 (1.6 to 12.7)		

Statistical analyses

Statistical analysis title	Progression free survival (RAS status)
Comparison groups	Mutant RAS v Wild-type RAS
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.037
Method	Logrank

Post-hoc: Overall survival (RAS status)	
End point title	Overall survival (RAS status)
End point description:	
End point type	Post-hoc
End point timeframe:	
At the end of follow-up.	

End point values	Mutant RAS	Wild-type RAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	15		
Units: months				
median (inter-quartile range (Q1-Q3))	7.3 (4.9 to 9.3)	12.3 (2.7 to 19.8)		

Statistical analyses

Statistical analysis title	Overall survival (RAS status)
Comparison groups	Wild-type RAS v Mutant RAS
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.745
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AEs were registered after the onset of the treatment.

Adverse event reporting additional description:

Only the frequency of grade 3/5 AEs is presented. In case of a patient has more than one AE with the same SOC, PT and different intensities, only the worst grade of toxicity has been counted (all occurrences).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Wild-type KRAS mCRC

Reporting group description: -

Serious adverse events	Wild-type KRAS mCRC		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 33 (36.36%)		
number of deaths (all causes)	28		
number of deaths resulting from adverse events	3		
Cardiac disorders			
Heart failure			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Confusional state			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Hemoglobin			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Obstruction gastric			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Rectal haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive airways disorder			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary thrombosis			
subjects affected / exposed	1 / 33 (3.03%)		
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	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Wound infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parotitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Wild-type KRAS mCRC		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 33 (30.30%)		
Cardiac disorders			
Ischaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Nervous system disorders			
Confusional state			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash: acne/acneiform			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Pruritus			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2009	After receiving the considerations of the participating Clinical Research Ethical Committees, changes were made in the Information Consent Form of the study as well as in the Information Consent Form of the optional biomarker study, aiming to facilitate their understanding.
29 July 2010	After the initial visits to the participating centers, it was found that some points of the protocol were not clear enough for the researchers. With this relevant modification it was clarified the doubts that arose as well as facilitated the work of the health professionals who carried out the study. 1. Permit the analysis of the KRAS gene by local laboratories according to their usual clinical practice, to determine the eligibility of the patients selected to participate in the trial. The reason for this modification was to minimize the delay in the initiation of treatment in patients who had this determination, since in the hospitals of the Spanish territory it is performed by usual clinical practice in patients with metastatic colorectal cancer. 2. Clarification of inclusion criteria nº 9 and nº 10. 3. Addition of an exclusion criterion. 4. The change of the principal investigator was requested, for reasons unrelated to the promoter, from one of the participating centers in the study: 5. Correction of a typographical error of one of the participating centers that was included in the request for evaluation of the clinical trial.
22 November 2012	The reason for this modification was to clarify on page 39 of the protocol, point 6.4. Treatment prohibited during the study period and correct typographical error that was a source of confusion for researchers.
22 July 2013	The objective of this modification was to change the principal investigator in one of the centers participating in the clinical trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations related to the study population and design of this exploratory phase II trial involving frail elderly patients.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25963019