Clinical trial results:
Randomised, multicentre, phase II pilot study to assess the safety and efficacy of treatment with mFOLFOX-6 plus cetuximab compared to initial treatment with mFOLFOX-6 plus cetuximab (for 8 cycles) followed by maintenance with cetuximab alone, as first line therapy in patients with metastatic colorectal cancer (mCRC) and wild-type KRAS tumours.

Summary

EudraCT number	2009-017194-38
Trial protocol	ES
Global end of trial date	28 May 2015

Results information

Result version number	v1 (current)
This version publication date	14 December 2018
First version publication date	14 December 2018

Trial information

Trial identification

Sponsor protocol code	TTD-09-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01161316
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Treatment of Digestive Tumours Group (TTD)
Sponsor organisation address	C/ Téllez nº30 posterior, planta 1ª, oficina 4-2/4-3, Madrid, Spain, 28007
Public contact	Inmaculada Ruiz Mena , Treatment of Digestive Tumours Group (TTD), +34 913788275, ttd@ttdgroup.org
Scientific contact	Inmaculada Ruiz Mena , Treatment of Digestive Tumours Group (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	04 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2015
Global end of trial reached?	Yes
Global end of trial date	28 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine non-inferiority in terms of progression-free survival from treatment with mFOLFOX-6 plus cetuximab until disease progression compared to initial treatment with mFOLFOX-6 plus cetuximab (8 cycles) followed by maintenance with cetuximab alone, as first-line treatment in patients with mCRC and KRAS wild-type tumours.

Protection of trial subjects:

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.

Background therapy:

Many studies with cetuximab as monotherapy or in combination with chemotherapeutic regimens prove the efficacy and safety of cetuximab in clinical practice, as first line treatment of metastatic colorectal cancer (mCRC). Accumulated evidences in chemotherapy-based maintenance therapy indicates that cetuximab as single-agent following induction chemotherapy in mCRC indicates that patients achieve a median progression free survival of 8.0 months and overall survival of 23.2 months. These evidences demonstrates that cetuximab may add benefit in the form of longer chemotherapy-free interval. Although, there is still a lack of evidence about the necessity to continuing treatment with chemotherapy to progression or unacceptable toxicity, several published studies explored the option of discontinuing chemotherapy followed by continuous cetuximab administration until disease progression to keep efficacy and reduce toxicity in comparison with the standard arm.

Evidence for comparator:

The potential of the single-agent maintenance regimen following initial combination chemotherapy has been evaluated for a number of agents. Single-agent maintenance therapy with capecitabine compared with capecitabine plus oxaliplatin or FOLFOX showed a significant prolonged PFS for patients receiving capecitabine compared with those receiving no active maintenance treatment (6.4 vs 3.4 months, respectively). In studies based on cetuximab administered as single-agent following oxaliplatin-based first-line therapy followed by cetuximab in patients with mCRC, showed median PFS and OS of 8.0 and 23.2 months respectively. Considering the mentioned results, this randomized phase II clinical trial was proposed, and based on the studies mentioned above, the control group will be patients treated with mFOLFOX-6 + cetuximab until progression.

Actual start date of recruitment	30 August 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 193

Worldwide total number of subjects	193
EEA total number of subjects	193

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)	84
From 65 to 84 years	109
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

193 patients were included; ITT (N=193) included 129 in experimental arm (arm A) and 64 in control arm (arm B), safety population included 127 in arm A and 62 in arm B, PP population included 110 in arm A and 54 in arm B. This was a national study with all patients being included at 25 Spanish sites.

Pre-assignment

Screening details:

Key inclusion criteria: male or female aged 18-71 years, ECOG ≤ 2, with metastatic colorectal carcinoma (WT KRAS) not prone to surgery, at least one measurable target lesion, life expectancy ≥12 weeks, no previous chemotherapy. Adequate bone marrow reserve and renal/liver functions. 194 patients were enrolled; 1 patient never received treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Single-agent Cetuximab

Arm description:

8 cycles of mFOLFOX-6 + cetuximab, followed by cetuximab (weekly dose of 250 mg/m2 by intravenous infusion over 60 minutes) alone until disease progression or early withdrawal.

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

Dosage and administration details:

Cetuximab was administered weekly. The first dose was 400 mg/m2 by intravenous infusion over 120 minutes; subsequent weekly doses were 250 mg/m2 by intravenous infusion over 60 minutes

Arm title	Arm B: mFOLFOX-6 + Cetuximab

Arm description:

mFOLFOX-6 + cetuximab until disease progression or early withdrawal. mFOLFOX-6 (biweekly) + cetuximab (weekly):
- cetuximab: weekly dose of 250 mg/m2 by intravenous infusion over 60 minutes
- oxaliplatin: intravenous infusion over 120 minutes on day 1
- folinic acid: 400 mg/m2 intravenous infusion over 120 minutes on day 1
- 5-fluorouracil: 400 mg/m2 bolus intravenous infusion on day 1 and then immediately start an infusion pump 2400 mg/m2 of 46 hours duration.

Arm type	Control
Investigational medicinal product name	mFOLFOX-6
Investigational medicinal product code	
Other name	oxaliplatin, folinic acid, 5-fluorouracil (5-FU)
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin administered at a dose of 85 mg/m2 on day 1, every 14 days by intravenous infusion, over 120 minutes. 5-Fluorouracil was administered at a dose of 400 mg/m2 on day 1, every 14 days as a bolus and immediately after an infusion pump was initiated at 2400 mg/m2 for 46 hours. Folinic acis was administered at a dose of 400 mg/m2 intravenous infusion in 120 minutes on day 1, every 14 days.

Number of subjects in period 1	Arm A: Single-agent Cetuximab	Arm B: mFOLFOX-6 + Cetuximab
Started	129	64
Completed	129	64

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Single-agent Cetuximab
Reporting group description:	
8 cycles of mFOLFOX-6 + cetuximab, followed by cetuximab (weekly dose of 250 mg/m2 by intravenous infusion over 60 minutes) alone until disease progression or early withdrawal.	
Reporting group title	Arm B: mFOLFOX-6 + Cetuximab
Reporting group description:	
mFOLFOX-6 + cetuximab until disease progression or early withdrawal. mFOLFOX-6 (biweekly) + cetuximab (weekly): - cetuximab: weekly dose of 250 mg/m2 by intravenous infusion over 60 minutes - oxaliplatin: intravenous infusion over 120 minutes on day 1 - folinic acid: 400 mg/m2 intravenous infusion over 120 minutes on day 1 - 5-fluorouracil: 400 mg/m2 bolus intravenous infusion on day 1 and then immediately start an infusion pump 2400 mg/m2 of 46 hours duration.	

Reporting group values	Arm A: Single-agent Cetuximab	Arm B: mFOLFOX-6 + Cetuximab	Total
Number of subjects	129	64	193
Age categorical			
Age for ITT population			
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
Adults (18-59 years)			0
Adults (60-79 years)			0
Age continuous			
Age for ITT population			
Units: years			
median	61	60	
full range (min-max)	33 to 74	34 to 73	-
Gender categorical			
Age for ITT population			
Units: Subjects			
Female	47	21	68
Male	82	43	125

End points

End points reporting groups

Reporting group title	Arm A: Single-agent Cetuximab
Reporting group description:	
8 cycles of mFOLFOX-6 + cetuximab, followed by cetuximab (weekly dose of 250 mg/m2 by intravenous infusion over 60 minutes) alone until disease progression or early withdrawal.	
Reporting group title	Arm B: mFOLFOX-6 + Cetuximab
Reporting group description:	
mFOLFOX-6 + cetuximab until disease progression or early withdrawal. mFOLFOX-6 (biweekly) + cetuximab (weekly): - cetuximab: weekly dose of 250 mg/m2 by intravenous infusion over 60 minutes - oxaliplatin: intravenous infusion over 120 minutes on day 1 - folinic acid: 400 mg/m2 intravenous infusion over 120 minutes on day 1 - 5-fluorouracil: 400 mg/m2 bolus intravenous infusion on day 1 and then immediately start an infusion pump 2400 mg/m2 of 46 hours duration.	
Subject analysis set title	KRAS wild-type - arm A (PP set)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects included in experimental arm	
Subject analysis set title	KRAS wild-type - arm B (PP Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subject included at control arm	
Subject analysis set title	RAS wild-type - arm A (PP Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subject included at experimental arm	
Subject analysis set title	RAS wild-type - arm B (PP Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects included at control arm	
Subject analysis set title	KRAS wild-type - arm A (ITT Set)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included at experimental arm	
Subject analysis set title	KRAS wild-type - arm B (ITT Set)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included at control arm	
Subject analysis set title	RAS wild-type - arm A (ITT Set)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included at experimental arm	
Subject analysis set title	RAS wild-type - arm B (ITT set)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects included at control arm	

Primary: Progression free survival

End point title	Progression free survival

End point description:

The percentage of patients free of progression and alive was estimated at 9 months and two-sided 95% confidence intervals (CI) of each treatment arm were calculated and 80% CI for non-inferiority. Progression-free survival time was defined as the number of months elapsed between the randomization date and the first evaluation of disease progression or until death of the patient, regardless of cause, irrelevant of the occurrence order. Kaplan-Meier method evaluated the survival distribution. The difference between the survival curves were tested by means of the Log Rank. HR and 95% CI were obtained using univariate Cox proportional hazard methods to estimate the treatment effect between the two treatment groups for progression free survival.

End point type	Primary

End point timeframe:

From treatment with mFOLFOX-6 plus cetuximab until disease progression.

End point values	KRAS wild-type - arm A (PP set)	KRAS wild-type - arm B (PP Set)	RAS wild-type - arm A (PP Set)	RAS wild-type - arm B (PP Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	110	54	80	44
Units: percent				
number (confidence interval 80%)				
PFS (%)	55 (46 to 65)	67 (56 to 79)	60 (49 to 71)	66 (51 to 81)

End point values	KRAS wild-type - arm A (ITT Set)	KRAS wild-type - arm B (ITT Set)	RAS wild-type - arm A (ITT Set)	RAS wild-type - arm B (ITT set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	129	64	92	44
Units: percent				
number (confidence interval 80%)				
PFS (%)	60 (52 to 69)	72 (61 to 83)	63 (53 to 73)	70 (57 to 84)

Statistical analyses

Statistical analysis title	Efficacy analysis (PP Set)
Comparison groups	KRAS wild-type - arm A (PP set) v KRAS wild-type - arm B (PP Set)
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0783
Method	Chi-squared
Parameter estimate	Difference in proportions
Point estimate	-0.11

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.2
upper limit	-0.02

Notes:

[1] - The significance level was 0.1 for the primary analysis.

Statistical analysis title	Efficacy analysis (PP Set)
Comparison groups	RAS wild-type - arm A (PP Set) v RAS wild-type - arm B (PP Set)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.0531
Method	Chi-squared
Parameter estimate	Difference in proportions
Point estimate	-0.06
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.18
upper limit	-0.06

Notes:

[2] - The significance level was 0.1 for the primary analysis.

Statistical analysis title	Efficacy analysis (ITT Set)
Comparison groups	KRAS wild-type - arm A (ITT Set) v KRAS wild-type - arm B (ITT Set)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.0502 [4]
Method	Chi-squared
Parameter estimate	Difference in proportions
Point estimate	-0.11
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.2
upper limit	-0.02

Notes:

[3] - The significance level was 0.1 for the primary analysis.

[4] - The significance level was 0.1 for the primary analysis.

Statistical analysis title	Efficacy analysis (ITT Set)

Statistical analysis description:

The significance level was 0.1 for the primary analysis.

Comparison groups	RAS wild-type - arm A (ITT Set) v RAS wild-type - arm B (ITT set)

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0581
Method	Chi-squared
Parameter estimate	Difference in proportions
Point estimate	-0.07
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.18
upper limit	0.04

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Overall survival time was calculated as the length of time in months between the date of randomization and death.

End point values	KRAS wild-type - arm A (ITT Set)	KRAS wild-type - arm B (ITT Set)	RAS wild-type - arm A (ITT Set)	RAS wild-type - arm B (ITT set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	129	64	92	44
Units: Months				
median (confidence interval 95%)				
OS (median)	23 (19 to 28)	27 (18 to 36)	25 (19 to 32)	28 (18 to 44)

Statistical analyses

Statistical analysis title	Efficacy analysis (ITT Set)
Comparison groups	KRAS wild-type - arm A (ITT Set) v KRAS wild-type - arm B (ITT Set)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2649
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.79

Statistical analysis title	Efficacy analysis (ITT Set)
Comparison groups	RAS wild-type - arm A (ITT Set) v RAS wild-type - arm B (ITT set)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3478
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.94

Secondary: Objective response rate

End point title	Objective response rate
End point description:	
The objective response rate was calculated using the RECIST v 1.1 criteria	
End point type	Secondary
End point timeframe:	
The objective response rate (ORR) was defined as the incidence of either a radiologically confirmed CR or PR.	

End point values	KRAS wild-type - arm A (ITT Set)	KRAS wild-type - arm B (ITT Set)	RAS wild-type - arm A (ITT Set)	RAS wild-type - arm B (ITT set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	129	64	92	44
Units: percent				
number (confidence interval 95%)				
ORR (%)	48 (39 to 57)	39 (27 to 52)	54 (44 to 65)	48 (33 to 62)

Statistical analyses

Statistical analysis title	Efficacy analysis (ITT Set)
Comparison groups	KRAS wild-type - arm B (ITT Set) v KRAS wild-type - arm A (ITT Set)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2368
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.66

Statistical analysis title	Efficacy analysis (ITT Set)
Comparison groups	RAS wild-type - arm A (ITT Set) v RAS wild-type - arm B (ITT set)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4696
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	2.68

Secondary: Median Progression-free survival	
End point title	Median Progression-free survival
End point description:	

End point type	Secondary
End point timeframe:	
From treatment with mFOLFOX-6 plus cetuximab until disease progression.	

End point values	KRAS wild-type - arm A (ITT Set)	KRAS wild-type - arm B (ITT Set)	RAS wild-type - arm A (ITT Set)	RAS wild-type - arm B (ITT set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	129	64	92	44
Units: Months				
median (confidence interval 95%)	9 (7 to 10)	10 (7 to 13)	9 (7 to 10)	10 (7 to 13)

Statistical analyses

Statistical analysis title	Efficacy analysis (ITT Set)
Comparison groups	KRAS wild-type - arm A (ITT Set) v KRAS wild-type - arm B (ITT Set)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3907
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.79

Statistical analysis title	Efficacy analysis (ITT Set)
Comparison groups	RAS wild-type - arm A (ITT Set) v RAS wild-type - arm B (ITT set)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.625
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.82

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:

Record AEs (day 1 of each cycle). 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	16.0

Reporting groups

Reporting group title	Arm-A

Reporting group description:

Experimental group

Reporting group title	Arm-B

Reporting group description:

Control group

Serious adverse events	Arm-A	Arm-B	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 127 (19.69%)	17 / 62 (27.42%)	
number of deaths (all causes)	92	40	
number of deaths resulting from adverse events	9	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis leak			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Overdose			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
femoral pseudoaneurysm			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thromboembolic event			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac and respiratory arrest			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 127 (0.79%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Nervous system disorders			
stroke			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
fever			
subjects affected / exposed	3 / 127 (2.36%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colonic obstruction			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 127 (3.15%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			

subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	5 / 127 (3.94%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	3 / 3	0 / 0	
Mucositis management			
subjects affected / exposed	1 / 127 (0.79%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
pulmonary thromboembolic event			
subjects affected / exposed	3 / 127 (2.36%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	3 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Prerenal failure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal failure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (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			
Encephalitis infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Lower respiratory tract infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 127 (0.00%)	4 / 62 (6.45%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	2 / 2	
Urinary tract infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Neutrophil count decreased			
subjects affected / exposed	2 / 127 (1.57%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 127 (0.79%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
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	89 / 127 (70.08%)	42 / 62 (67.74%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	36 / 127 (28.35%)	16 / 62 (25.81%)	
occurrences (all)	36	16	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 127 (8.66%)	3 / 62 (4.84%)	
occurrences (all)	11	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 127 (7.09%)	5 / 62 (8.06%)	
occurrences (all)	9	5	
Mucositis management			
subjects affected / exposed	9 / 127 (7.09%)	4 / 62 (6.45%)	
occurrences (all)	9	4	
Skin and subcutaneous tissue disorders			
rash acneiform			
subjects affected / exposed	19 / 127 (14.96%)	15 / 62 (24.19%)	
occurrences (all)	19	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2010	Due to a request for clarification from the EIC, the PIS, IC and the protocol were modified. Corrections of typographical errors in the protocol were performed. The Version 1.1 of the RECIST criteria in the protocol was updated.
25 June 2010	Following the protocol evaluation of AEMPS and the proofs received, a series of important modification were performed to the protocol: - Due to occurrence of cardiac toxicity cases in previous clinical trials performed with cetuximab + FOLFOX, an additional program carefully monitoring cardiac function of both arms was suggested. However the applied regimen for the treatment of metastatic colorectal cancer is a well-established one where monitoring cardiac function is unnecessary. - As suggested by AEMPS the inclusion criteria were modified with the aim of shortening the maximum age of participation to <71 years of age. - With the aim of clarifying certain points of the protocol, typographical errors were detected and amended. Information in some paragraphs was also updated.
01 October 2010	The centre Hospital Reina Sofía de Córdoba was incorporated into the study.
04 February 2011	To change the principal investigator of two of the centres participating in the clinical trial: Hospital de Navarra and Hospital General de Cataluña as well as the formal notification of the non-participation of the centres: Hospital de Donostia, Hospital Virgen de la Arrixaca and Hospital de León.
30 May 2011	The addition of an open, biological, multicentre prospective substudy, which was undertaken simultaneously with the clinical trial TTD-09-04 entitled "Study of circulating tumour cells in patient´s peripheral blood with metastatic colorectal adenocarcinoma". This study quantified circulating tumour cells in the patient´s peripheral blood with metastatic colorectal adenocarcinoma at baseline.
27 September 2011	To change the principal investigator of the centre Hospital Nuestra Señora de Cadelaria participating in this study.
31 May 2012	A change in the patient´s informed consent sheet was performed altering safety information relevant for cetuximab.
28 January 2013	To clarify certain points of the protocol, update the information on some sections and correct any errors that were observed in the previous version of the protocol. A new version of the protocol was generated, v.5.0 dated 28th January 2013.
03 September 2013	To change the principal investigator of the centre Hospital Universitario 12 de Octubre participating in this study.
21 March 2014	To include in the study protocol the determination of the biomarkers KRAS (exons 3 and 4), NRAS (exons 2, 3 and 4) with the aim of obtaining additional information on the correlation between efficacy variables (progression-free survival, overall survival, objective response rate and resectability of disease) and RAS mutational status. Recent publications have led to a modification of the anti-EGFR drug indications (cetuximab and panitumumab) and the analysis of RAS mutational status, making this analysis compulsory for the administration of any anti-EGFR therapy. It is for this reason that the clinical benefit of the administered treatment was analysed in the context of the MACRO2 trial in accordance to the new biomarker.

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.

Limited sample size and the relaxed significance level of one-sided alpha of 0.1 for non-inferiority testing.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30054049