Clinical trial results:
Open, multicenter phase II study to evaluate the efficacy and safety of the combination of Panitumumab with Irinotecan in patients with Wild-Type KRAS metastatic colorectal cancer refractory to irinotecan based chemotherapy

Summary

EudraCT number	2009-010833-27
Trial protocol	ES
Global end of trial date	31 July 2014

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020

Trial information

Trial identification

Sponsor protocol code	TTD08-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00958386
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	17 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2014
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 effect of the combination of panitumumab with irinotecan in tumour response rate, defined as partial and complete response according to modified RECIST criteria, in subjects with wild-type KRAS mCRC refractory to irinotecan based chemotherapy.

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. The use of topical, oral or IV antibiotics to treat skin- or nail-related toxicities at allowed at the investigator's discretion. For subjects on anticoagulant therapy, close monitoring of coagulation parameters was recommended during the study treatment period. For low white blood cell counts, granulocyte-colony-stimulating factor (G-CSF) should be used; however, routine prophylactic use of G-CSF was not recommended on this trial. Therapeutic G-CSF use in patients with serious neutropenic complications such as tissue infections, sepsis syndrome, fungal infection, etc., was allowed at the investigator's discretion or according to institutional standards. Regional variations in the practice were acceptable. Epoetins were allowed at the investigator's discretion to treat chemotherapy-induced anaemia.

Background therapy:

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. Panitumumab provides an ORR of 17% in patients refractory to irinotecan-based chemotherapy. In this setting, the ORR of the combination of irinotecan and panitumumab is expected to be around 30%. The hypothesis is that the benefits of an irinotecan therapy might be recovered in irinotecan-refractory patients through the use of panitumumab as it has been clearly shown with cetuximab.

Evidence for comparator:

Not applicable

Actual start date of recruitment	24 July 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	28
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 61 patients were enrolled in the study: 40 males and 21 females. The median age was 65.5 (range, 40-81) years. All the patients were Caucasian. This was a national study with all patients being included at 16 Spanish sites.

Pre-assignment

Screening details:

Patients were required to have received irinotecan for at least 6 weeks, with no more than 2 dose reductions, with one or more measurable lesion, a Karnofsky performance status of at least 70%, adequate hematologic, hepatic, and renal function, and serum magnesium and calcium levels within normal limits. Prior anti-EGFR therapy was not permitted.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

Arm title	Wild-type KRAS mCRC

Arm description:

Wild-type KRAS mCRC patients. Panitumumab was administered by intravenous (IV) infusion at a dose of 6 mg/kg once Q2W. Irinotecan chemotherapy at a dose of 180 mg/m2 Q2W, or the last pre-study irinotecan dose, was administered after the administration of panitumumab.

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

Dosage and administration details:

Patients received panitumumab (6 mg/kg, 60-min infusion) followed by irinotecan (180 mg/m², 90-min infusion) every 2 weeks. For patients who had received a reduced dose with prior irinotecan therapy, this dose was maintained, and for patients who had received 350 mg/m² irinotecan every 3 weeks, the equivalent every-2-weeks dose was used.

Number of subjects in period 1	Wild-type KRAS mCRC
Started	61
Completed	61

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description: Wild-type KRAS mCRC	

Reporting group values	Baseline	Total	
Number of subjects	61	61	
Age categorical Units: Subjects			
Adults (18-64 years)	28	28	
From 65-84 years	33	33	
Age continuous Units: years			
median	65.4		
full range (min-max)	40 to 81	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	40	40	

Subject analysis sets	
Subject analysis set title	Wild-type KRAS mCRC
Subject analysis set type	Sub-group analysis
Subject analysis set description: Wild-type KRAS mCRC patients.	
Subject analysis set title	Wild-type RAS
Subject analysis set type	Sub-group analysis
Subject analysis set description: Wild-type KRAS mCRC patients.	
Subject analysis set title	Mutated RAS
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with mutant RAS	
Subject analysis set title	Wild-type BRAF
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with wild-type BRAF	
Subject analysis set title	Mutated BRAF
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with mutant BRAF	
Subject analysis set title	Wild-type PI3KCA
Subject analysis set type	Sub-group analysis
Subject analysis set description: Wild-type PI3KCA patients	
Subject analysis set title	Mutated PI3KCA

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Mutated PI3KCA patients	
Subject analysis set title	Epiregulin (low expression)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with low expression of epiregulin.	
Subject analysis set title	Epiregulin (high expression)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with high expression of epiregulin.	
Subject analysis set title	Amphiregulin (low expression)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with low amphiregulin expression	
Subject analysis set title	Amphiregulin (high expression)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with high amphiregulin expression.	
Subject analysis set title	EGFR positive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with EGFR gene amplification.	
Subject analysis set title	EGFR negative
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with no EGFR expression.	
Subject analysis set title	PTEN positive (1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with PTEN gene expression.	
Subject analysis set title	PTEN negative (0)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with no PTEN expression.	

Reporting group values	Wild-type KRAS mCRC	Wild-type RAS	Mutated RAS
Number of subjects	61	46	11
Age categorical Units: Subjects			
Adults (18-64 years)	28		
From 65-84 years	33		
Age continuous Units: years			
median	65.4		
full range (min-max)	40 to 81		
Gender categorical Units: Subjects			
Female	21		
Male	40		

Reporting group values	Wild-type BRAF	Mutated BRAF	Wild-type PI3KCA
Number of subjects	54	4	49
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

Reporting group values	Mutated PI3KCA	Epiregulin (low expression)	Epiregulin (high expression)
Number of subjects	8	17	18
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

Reporting group values	Amphiregulin (low expression)	Amphiregulin (high expression)	EGFR positive
Number of subjects	17	18	3
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

Reporting group values	EGFR negative	PTEN positive (1)	PTEN negative (0)
Number of subjects	31	9	23
Age categorical Units: Subjects			
Adults (18-64 years)			

From 65-84 years			

Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Wild-type KRAS mCRC
Reporting group description:	
Wild-type KRAS mCRC patients. Panitumumab was administered by intravenous (IV) infusion at a dose of 6 mg/kg once Q2W. Irinotecan chemotherapy at a dose of 180 mg/m2 Q2W, or the last pre-study irinotecan dose, was administered after the administration of panitumumab.	
Subject analysis set title	Wild-type KRAS mCRC
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Wild-type KRAS mCRC patients.	
Subject analysis set title	Wild-type RAS
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Wild-type KRAS mCRC patients.	
Subject analysis set title	Mutated RAS
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with mutant RAS	
Subject analysis set title	Wild-type BRAF
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with wild-type BRAF	
Subject analysis set title	Mutated BRAF
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with mutant BRAF	
Subject analysis set title	Wild-type PI3KCA
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Wild-type PI3KCA patients	
Subject analysis set title	Mutated PI3KCA
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Mutated PI3KCA patients	
Subject analysis set title	Epiregulin (low expression)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with low expression of epiregulin.	
Subject analysis set title	Epiregulin (high expression)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with high expression of epiregulin.	
Subject analysis set title	Amphiregulin (low expression)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with low amphiregulin expression	
Subject analysis set title	Amphiregulin (high expression)
Subject analysis set type	Sub-group analysis

Subject analysis set description:	
Patients with high amphiregulin expression.	
Subject analysis set title	EGFR positive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with EGFR gene amplification.	
Subject analysis set title	EGFR negative
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with no EGFR expression.	
Subject analysis set title	PTEN positive (1)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with PTEN gene expression.	
Subject analysis set title	PTEN negative (0)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with no PTEN expression.	

Primary: Overall response rate (ORR)

End point title	Overall response rate (ORR)[1]
End point description:	
End point type	Primary
End point timeframe:	
The incidence of either a radiologically confirmed complete response (CR) or partial response (PR).	

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 analyses for this end point were performed since it was a single-arm study.

End point values	Wild-type KRAS mCRC	Wild-type RAS	Mutated RAS	Wild-type BRAF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	46	11	54
Units: percent				
number (confidence interval 95%)	13.1 (4.6 to 21.6)	15.2 (4.8 to 25.6)	9.1 (0.0 to 26.1)	13.0 (4.0 to 21.9)

End point values	Mutated BRAF	Wild-type PI3KCA	Mutated PI3KCA	Epiregulin (low expression)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	49	8	17
Units: percent				
number (confidence interval 95%)	25.0 (0.0 to 67.4)	14.3 (4.5 to 24.1)	12.5 (0.0 to 35.4)	11.8 (0.0 to 27.1)

End point values	Epiregulin	Amphiregulin	Amphiregulin	EGFR positive

	(high expression)	(low expression)	(high expression)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	17	18	3
Units: percent				
number (confidence interval 95%)	16.7 (0.0 to 33.9)	5.9 (0.0 to 17.1)	22.2 (3.0 to 41.4)	0 (0.0 to 0.0)

End point values	EGFR negative	PTEN positive (1)	PTEN negative (0)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	31	9	23	
Units: percent				
number (confidence interval 95%)	16.1 (3.2 to 29.1)	0 (0.0 to 0.0)	21.7 (4.9 to 38.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

The number of days between the date of inclusion and the time of the first assessment of progressive disease (PD) or death (whichever comes first) during the treatment phase.

End point values	Wild-type KRAS mCRC	Wild-type RAS	Mutated RAS	Wild-type BRAF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	46	11	54
Units: percent				
median (confidence interval 95%)	3.7 (2.7 to 4.2)	3.8 (2.7 to 4.3)	2.9 (1.4 to 4.6)	3.7 (2.7 to 4.2)

End point values	Mutated BRAF	Wild-type PI3KCA	Mutated PI3KCA	Epiregulin (low expression)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	49	8	17
Units: percent				
median (confidence interval 95%)	1.8 (0.7 to 6.4)	3.9 (2.9 to 4.3)	2.7 (0.7 to 5.7)	2.9 (1.4 to 4.8)

End point values	Epiregulin (high expression)	Amphiregulin (low expression)	Amphiregulin (high expression)	EGFR positive
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	17	18	3
Units: percent				
median (confidence interval 95%)	3.9 (2.7 to 4.6)	2.7 (1.4 to 3.6)	4.3 (3.0 to 5.4)	2.9 (2.7 to 3.6)

End point values	EGFR negative	PTEN positive (1)	PTEN negative (0)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	31	9	23	
Units: percent				
median (confidence interval 95%)	3.7 (1.6 to 4.6)	4.1 (0.7 to 4.9)	3.0 (1.6 to 4.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (at 60 days)

End point title	Progression free survival (at 60 days)

End point description:

End point type	Secondary

End point timeframe:

From inclusion and the time of the first assessment of PD according to modified RECIST criteria or death (whichever comes first) during the 60 days after the last evaluable tumour assessment or the date of inclusion (whichever occurs last).

End point values	Wild-type KRAS mCRC			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: Percent				
median (confidence interval 95%)	3.7 (2.7 to 4.2)			

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:

During the treatment phase of combination therapy.

End point values	Wild-type KRAS mCRC			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: percent				
median (confidence interval 95%)	62.3 (50.1 to 74.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

End point type	Secondary

End point timeframe:

From the date of first confirmed response and the time of the first assessment of PD or death due to disease progression (if this occurs earlier) in the subgroup of patients that respond to treatment.

End point values	Wild-type KRAS mCRC			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: percent				
median (confidence interval 95%)	3.5 (1.6 to 4.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response

End point title	Time to response

End point description:

End point type	Secondary

End point timeframe:

From the date of enrollment to the first confirmed CR or PR.

End point values	Wild-type KRAS mCRC			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: Months				
arithmetic mean (standard error)	5.1 (± 0.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

End point type	Secondary

End point timeframe:

From the inclusion and the time of the first assessment of progressive disease in this study or until death due to progression (whichever was earlier) during the study.

End point values	Wild-type KRAS mCRC			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: Months				
median (confidence interval 95%)	3.7 (2.7 to 4.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of stable disease

End point title	Duration of stable disease

End point description:

End point type	Secondary

End point timeframe:

From inclusion in the study and the time of the first assessment of PD or death due to disease progression (if this occurred before) in the subgroup of patients with CR, PR or SD as best response during the treatment phase.

End point values	Wild-type KRAS mCRC			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: Months				
median (confidence interval 95%)	3.0 (2.1 to 3.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

End point type	Secondary

End point timeframe:

From inclusion and the date on which the decision to end treatment was taken, for any reason. In patients who remained in the treatment phase at the time of analysis, it was registered at the date of last evaluation during the study.

End point values	Wild-type KRAS mCRC			
Subject group type	Subject analysis set			
Number of subjects analysed	61			
Units: Months				
median (confidence interval 95%)	2.8 (1.8 to 3.7)			

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:

From inclusion to the date of death for any reason defined.

End point values	Wild-type KRAS mCRC	Wild-type RAS	Mutated RAS	Wild-type BRAF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	46	11	54
Units: Months				
median (confidence interval 95%)	11.1 (7.1 to 14.8)	12.5 (6.7 to 15.9)	11.1 (4.2 to 23.9)	12.5 (7.1 to 15.7)

End point values	Mutated BRAF	Wild-type PI3KCA	Mutated PI3KCA	Epiregulin (low expression)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	49	8	17
Units: Months				
median (confidence interval 95%)	6.7 (3.9 to 7.4)	11.1 (6.7 to 15.6)	14.8 (2.7 to 19.0)	15.9 (6.7 to 19.1)

End point values	Epiregulin (high expression)	Amphiregulin (low expression)	Amphiregulin (high expression)	EGFR positive
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	18	17	18	3
Units: Months				
median (confidence interval 95%)	13.5 (6.0 to 22.7)	10.8 (5.1 to 14.8)	15.9 (11.1 to 22.3)	12.2 (5.1 to 17.0)

End point values	EGFR negative	PTEN positive (1)	PTEN negative (0)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	31	9	23	
Units: Months				
median (confidence interval 95%)	14.8 (10.2 to 19.1)	14.8 (8.6 to 29.2)	13.7 (6.0 to 19.1)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) reported after initiation of treatment with study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Wild-type KRAS

Reporting group description: -

Serious adverse events	Wild-type KRAS		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 61 (31.15%)		
number of deaths (all causes)	56		
number of deaths resulting from adverse events	3		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Keratitis			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal toxicity			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	1 / 61 (1.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Wild-type KRAS		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 61 (70.49%)		
Congenital, familial and genetic disorders			

Trichomegaly subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 6		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	 9 / 61 (14.75%) 17 6 / 61 (9.84%) 6		
General disorders and administration site conditions Intestinal obstruction subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) Mucosal inflammation subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 5 / 61 (8.20%) 5 36 / 61 (59.02%) 54 18 / 61 (29.51%) 27 6 / 61 (9.84%) 7 7 / 61 (11.48%) 8		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	 9 / 61 (14.75%) 11		
Gastrointestinal disorders Ascites subjects affected / exposed occurrences (all) Abdominal pain	 4 / 61 (6.56%) 4 		

subjects affected / exposed	12 / 61 (19.67%)		
occurrences (all)	15		
Constipation			
subjects affected / exposed	7 / 61 (11.48%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	17 / 61 (27.87%)		
occurrences (all)	26		
Vomiting			
subjects affected / exposed	18 / 61 (29.51%)		
occurrences (all)	24		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	8		
Cough			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	11 / 61 (18.03%)		
occurrences (all)	13		
Alopecia			
subjects affected / exposed	12 / 61 (19.67%)		
occurrences (all)	14		
Dry skin			
subjects affected / exposed	16 / 61 (26.23%)		
occurrences (all)	17		
Erythema			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	7		
Pruritus			
subjects affected / exposed	6 / 61 (9.84%)		
occurrences (all)	7		
Rash			

subjects affected / exposed	34 / 61 (55.74%)		
occurrences (all)	21		
Skin fissures			
subjects affected / exposed	5 / 61 (8.20%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 61 (11.48%)		
occurrences (all)	7		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 61 (6.56%)		
occurrences (all)	4		
Paronychia			
subjects affected / exposed	13 / 61 (21.31%)		
occurrences (all)	14		
Respiratory tract infection			
subjects affected / exposed	5 / 61 (8.20%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 61 (21.31%)		
occurrences (all)	18		
Hypokalaemia			
subjects affected / exposed	7 / 61 (11.48%)		
occurrences (all)	8		
Hypomagnesaemia			
subjects affected / exposed	28 / 61 (45.90%)		
occurrences (all)	32		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2009	The aim of this amendment was to include some clarifications in the informed consent sheet requested by the IRB/IECs in order to facilitate its understanding, and in the study protocol.
29 May 2009	By means of this amendment four centres were included to participate in the study.
24 November 2010	By means of this amendment change, the determination of the mutational status of KRAS could be performed according to routine clinical practice in local laboratories in order to determine patients' eligibility for this trial. The reason for this amendment was to minimize the delay in starting treatment in patients who had this determination, since this was performed by standard clinical practice in Spain in patients with metastatic colorectal cancer. Additionally, one centre was removed from the study.
28 February 2011	With this protocol amendment, information sheet was updated according to the panitumumab safety updating.
22 July 2013	The purpose of this amendment was to change the principal investigator of three of the centres 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.

None reported.

Notes: