Clinical trial results:
An Open label Randomized Multi-Centre Exploratory Phase II Study to Evaluate the Efficacy and Safety of the Combination of Panitumumab with FOLFOX 4 Chemotherapy or Panitumumab with FOLFIRI Chemotherapy in Subjects with Wild-Type KRAS Colorectal Cancer and Liver-only Metastases

Summary

EudraCT number	2008-006766-28
Trial protocol	ES
Global end of trial date	31 March 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-08-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00885885
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)
Sponsor organisation address	Téllez 30, Madrid, Spain, 28007
Public contact	Inmaculada Ruiz Mena, Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD), 0034 913788275, ttd@ttdgroup.org
Scientific contact	Inmaculada Ruiz Mena, Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD), 0034 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	26 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2013
Global end of trial reached?	Yes
Global end of trial date	31 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the objective response rate (ORR) over the entire treatment period when panitumumab was administered in combination with either FOLFOX 4 or FOLFIRI chemotherapy as 1st line treatment in subjects with previously untreated KRAS Wild-Type colorectal cancer (mCRC) and liver-only metastases. To determine the optimal combination (panitumumab + FOLFOX 4 chemotherapy or panitumumab + FOLFIRI chemotherapy) based on efficacy and tolerability for further clinical trials in this population.

Protection of trial subjects:

Treatment dose was adjusted in terms of adverse events. G-CSF as prophylaxis was not recommended; G-CSF could be used therapeutically at the Investigator’s discretion in patients with serious neutropenic complications. The use of topical, oral, and intravenous antibiotics to treat skin- and nail-related toxicities was allowed at the Investigator’s discretion.

Background therapy:

None.

Evidence for comparator:

While there have been few prospective studies of systemic chemotherapy in patients with non-resectable hepatic metastases, it seems clear that the use of FOLFOX and FOLFIRI combination chemotherapy regimens with biological therapies, especially EGFR inhibitors, can increase the response rate

Actual start date of recruitment	14 May 2009
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: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	45
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

80 patients were included; 3 of them did not receive any study treatment. The safety population included 38 patients in the Panitumumab + FOLFOX-4 arm and 39 patients in the Panitumumab + FOLFIRI arm. This was a national study with all patients being included at 15 Spanish sites

Pre-assignment

Screening details:

Key inclusion criteria: Male or female > 18 years of age, histologically confirmed adenocarcinoma of the colon or rectum with liver-only metastases, no major contraindication to liver surgery, wild-type KRAS. 103 patients were assessed for eligibility, of whom 21 did not meet all the inclusion criteria and 2 met one of the exclusion criteria.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Panitumumab + FOLFOX 4

Arm description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and commencement of FOLFOX 4 chemotherapy. FOLFOX 4 was administered every 2 weeks (± 3 days) as follows:
Day 1: Oxaliplatin (85 mg/m2, intravenous infusion) and folinic acid (200 mg/m2, intravenous infusion), both given over 120 minutes (± 15 minutes) at the same time; followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2, intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.
Day 2: Folinic acid (200 mg/m2, intravenous infusion), given over 120 minutes (± 15 minutes); followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2 intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.

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

Dosage and administration details:

The starting panitumumab dose was 6 mg/kg. The panitumumab dose was calculated based on the subject’s body weight at baseline (i.e. Cycle 1) and was not re-calculated unless the actual body weight changed by at least 10% relative to baseline. Panitumumab was diluted in 100 mL of pyrogen-free 0.9% sodium chloride solution. The maximum concentration of the diluted solution to be infused was not to exceed 10 mg/mL; if necessary, the volume of normal saline could be increased. Panitumumab was administered intravenously using an infusion pump.

Investigational medicinal product name	FOLFOX 4
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous use, Intravenous bolus use

Dosage and administration details:

FOLFOX 4 was administered as follows:
Day 1: Oxaliplatin (85 mg/m2, intravenous infusion) and folinic acid (200 mg/m2, intravenous infusion), both given over 120 minutes (± 15 minutes) at the same time; followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2, intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.
Day 2: Folinic acid (200 mg/m2, intravenous infusion), given over 120 minutes (± 15 minutes); followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2 intravenous infusion), given as a 22-hour (± 1 hour) continuous infusion.

Arm title	Panitumumab + FOLFIRI

Arm description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and FOLFIRI chemotherapy. FOLFIRI was administered every 2 weeks (± 3 days), on day 1 of each cycle, as follows: Irinotecan (180 mg/m2, intravenous infusion) was administered over 90 minutes (± 15 minutes). Folinic acid (400 mg/m2, intravenous infusion) was administered over 2 hours (± 15 minutes) during Irinotecan infusion, but without mixing. Immediately afterwards, a 5-FU intravenous bolus (400 mg/m2) was administered and a 5-FU intravenous infusion (2400 mg/m2) was given as a 46 hour (± 2-hour) continuous infusion.

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

Dosage and administration details:

The starting panitumumab dose was 6 mg/kg. The panitumumab dose was calculated based on the subject’s body weight at baseline (i.e. Cycle 1) and was not re-calculated unless the actual body weight changed by at least 10% relative to baseline. Panitumumab was diluted in 100 mL of pyrogen-free 0.9% sodium chloride solution. The maximum concentration of the diluted solution to be infused was not to exceed 10 mg/mL; if necessary, the volume of normal saline could be increased. Panitumumab was administered intravenously using an infusion pump.

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

FOLFIRI was administered on day 1 of each cycle as follows:
Irinotecan (180 mg/m2, intravenous infusion) was administered over 90 minutes ± 15 minutes. Folinic acid (400 mg/m2, intravenous infusion) was administered over 2 hours ± 15 minutes during irinotecan infusion. but without mixing. Immediately afterwards, a 5-FU intravenous bolus (400 mg/m2) was administered and a 5-FU intravenous infusion (2400 mg/m2) was given as 46-hour ± 2-hour continuous infusion.

Number of subjects in period 1[1]	Panitumumab + FOLFOX 4	Panitumumab + FOLFIRI
Started	38	39
Completed	38	39

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 3 patients in Panitumumab + FOLFIRI arm were withdrawn from the study without receiving study treatment: 1 patient had divergent KRAS results and 2 patients had metastases in locations other than the liver. These 3 patients are not included in the presentations of Subject disposition, Baseline characteristics, End points and Adverse events.

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Panitumumab + FOLFOX 4

Arm description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and commencement of FOLFOX 4 chemotherapy. FOLFOX 4 was administered every 2 weeks (± 3 days) as follows:
Day 1: Oxaliplatin (85 mg/m2, intravenous infusion) and folinic acid (200 mg/m2, intravenous infusion), both given over 120 minutes (± 15 minutes) at the same time; followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2, intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.
Day 2: Folinic acid (200 mg/m2, intravenous infusion), given over 120 minutes (± 15 minutes); followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2 intravenous infusion), given as a 22-hour (± 1 hour) continuous infusion.

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

Dosage and administration details:

The starting panitumumab dose was 6 mg/kg. The panitumumab dose was calculated based on the subject’s body weight at baseline (i.e. Cycle 1) and was not re-calculated unless the actual body weight changed by at least 10% relative to baseline. Panitumumab was diluted in 100 mL of pyrogen-free 0.9% sodium chloride solution. The maximum concentration of the diluted solution to be infused was not to exceed 10 mg/mL; if necessary, the volume of normal saline could be increased. Panitumumab was administered intravenously using an infusion pump.

Investigational medicinal product name	FOLFOX 4
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous use, Intravenous bolus use

Dosage and administration details:

FOLFOX 4 was administered as follows:
Day 1: Oxaliplatin (85 mg/m2, intravenous infusion) and folinic acid (200 mg/m2, intravenous infusion), both given over 120 minutes (± 15 minutes) at the same time; followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2, intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.
Day 2: Folinic acid (200 mg/m2, intravenous infusion), given over 120 minutes (± 15 minutes); followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2 intravenous infusion), given as a 22-hour (± 1 hour) continuous infusion.

Arm title	Panitumumab + FOLFIRI

Arm description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and FOLFIRI chemotherapy. FOLFIRI was administered every 2 weeks (± 3 days), on day 1 of each cycle, as follows: Irinotecan (180 mg/m2, intravenous infusion) was administered over 90 minutes ± 15 minutes. Folinic acid (400 mg/m2, intravenous infusion) was administered over 2 hours ± 15 minutes during irinotecan infusion. but without mixing. Immediately afterwards, a 5-FU intravenous bolus (400 mg/m2) was administered and a 5-FU intravenous infusion (2400 mg/m2) was given as 46-hour ± 2 hour continuous infusion.

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

Dosage and administration details:

The starting panitumumab dose was 6 mg/kg. The panitumumab dose was calculated based on the subject's body weight at baseline (i.e. Cycle 1) and was not re-calculated unless the actual body weight changed by at least 10% relative to baseline. Panitumumab was diluted in 100 mL of pyrogen-free 0.9% sodium chloride solution. The maximum concentration of the diluted solution to be infused was not to exceed 10 mg/mL; if necessary, the volume of normal saline could be increased. Panitumumab was administered intravenously using an infusion pump.

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

FOLFIRI was administered on day 1 of each cycle as follows:
Irinotecan (180 mg/m2, intravenous infusion) was administered over 90 minutes ± 15 minutes. Folinic acid (400 mg/m2, intravenous infusion) was administered over 2 hours ± 15 minutes during irinotecan infusion. but without mixing. Immediately afterwards, a 5-FU intravenous bolus (400 mg/m2) was administered and a 5-FU intravenous infusion (2400 mg/m2) was given as 46-hour ± 2-hour continuous infusion.

Number of subjects in period 2	Panitumumab + FOLFOX 4	Panitumumab + FOLFIRI
Started	38	39
Completed	10	10
Not completed	28	29
Physician decision	3	9
Disease progression	13	11
Other	3	4
Death	-	2
Adverse event	1	1
Unacceptable toxicity	7	2
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Panitumumab + FOLFOX 4

Reporting group description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and commencement of FOLFOX 4 chemotherapy. FOLFOX 4 was administered every 2 weeks (± 3 days) as follows:
Day 1: Oxaliplatin (85 mg/m2, intravenous infusion) and folinic acid (200 mg/m2, intravenous infusion), both given over 120 minutes (± 15 minutes) at the same time; followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2, intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.
Day 2: Folinic acid (200 mg/m2, intravenous infusion), given over 120 minutes (± 15 minutes); followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2 intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.

Reporting group title	Panitumumab + FOLFIRI

Reporting group description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and FOLFIRI chemotherapy. FOLFIRI was administered every 2 weeks (± 3 days), on day 1 of each cycle, as follows: Irinotecan (180 mg/m2, intravenous infusion) was administered over 90 minutes (± 15 minutes). Folinic acid (400 mg/m2, intravenous infusion) was administered over 2 hours (± 15 minutes) during Irinotecan infusion, but without mixing. Immediately afterwards, a 5-FU intravenous bolus (400 mg/m2) was administered and a 5-FU intravenous infusion (2400 mg/m2) was given as a 46 hour (± 2-hour) continuous infusion.

Reporting group values	Panitumumab + FOLFOX 4	Panitumumab + FOLFIRI	Total
Number of subjects	38	39	77
Age categorical 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
Age continuous Units: years			
median	65.2	62.6	
inter-quartile range (Q1-Q3)	57.9 to 70.1	51.9 to 67.4	-
Gender categorical Units: Subjects			
Female	7	11	18
Male	31	28	59

End points

End points reporting groups

Reporting group title	Panitumumab + FOLFOX 4

Reporting group description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and commencement of FOLFOX 4 chemotherapy. FOLFOX 4 was administered every 2 weeks (± 3 days) as follows:
Day 1: Oxaliplatin (85 mg/m2, intravenous infusion) and folinic acid (200 mg/m2, intravenous infusion), both given over 120 minutes (± 15 minutes) at the same time; followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2, intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.
Day 2: Folinic acid (200 mg/m2, intravenous infusion), given over 120 minutes (± 15 minutes); followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2 intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.

Reporting group title	Panitumumab + FOLFIRI

Reporting group description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and FOLFIRI chemotherapy. FOLFIRI was administered every 2 weeks (± 3 days), on day 1 of each cycle, as follows: Irinotecan (180 mg/m2, intravenous infusion) was administered over 90 minutes (± 15 minutes). Folinic acid (400 mg/m2, intravenous infusion) was administered over 2 hours (± 15 minutes) during Irinotecan infusion, but without mixing. Immediately afterwards, a 5-FU intravenous bolus (400 mg/m2) was administered and a 5-FU intravenous infusion (2400 mg/m2) was given as a 46 hour (± 2-hour) continuous infusion.

Reporting group title	Panitumumab + FOLFOX 4

Reporting group description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and commencement of FOLFOX 4 chemotherapy. FOLFOX 4 was administered every 2 weeks (± 3 days) as follows:
Day 1: Oxaliplatin (85 mg/m2, intravenous infusion) and folinic acid (200 mg/m2, intravenous infusion), both given over 120 minutes (± 15 minutes) at the same time; followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2, intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.
Day 2: Folinic acid (200 mg/m2, intravenous infusion), given over 120 minutes (± 15 minutes); followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2 intravenous infusion), given as a 22-hour (± 1 hour) continuous infusion.

Reporting group title	Panitumumab + FOLFIRI

Reporting group description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and FOLFIRI chemotherapy. FOLFIRI was administered every 2 weeks (± 3 days), on day 1 of each cycle, as follows: Irinotecan (180 mg/m2, intravenous infusion) was administered over 90 minutes ± 15 minutes. Folinic acid (400 mg/m2, intravenous infusion) was administered over 2 hours ± 15 minutes during irinotecan infusion. but without mixing. Immediately afterwards, a 5-FU intravenous bolus (400 mg/m2) was administered and a 5-FU intravenous infusion (2400 mg/m2) was given as 46-hour ± 2 hour continuous infusion.

Subject analysis set title	Panitumumab + FOLFOX 4 (Safety Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects in the Panitumumab + FOLFOX 4 arm who received at least one dose of Panitumumab or FOLFOX 4 chemotherapy.

Subject analysis set title	Panitumumab + FOLFIRI (Safety Set)
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects in the Panitumumab + FOLFIRI arm who received at least one dose of Panitumumab or FOLFIRI chemotherapy.

Subject analysis set title	Panitumumab + FOLFOX 4 (WT RAS Set)

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects in the Panitumumab + FOLFOX 4 (Safety Set) analysis set whose RAS mutational status was evaluated and was found to be wild type.	
Subject analysis set title	Panitumumab + FOLFIRI (WT RAS Set)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects in the Panitumumab + FOLFIRI (Safety Set) analysis set whose RAS mutational status was evaluated and was found to be wild type.	
Subject analysis set title	All subjects (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized subjects who received at least one dose of Panitumumab or FOLFOX 4 chemotherapy or FOLFIRI chemotherapy.	
Subject analysis set title	All subjects (WT RAS Set)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects in the All patients (Safety Set) analysis set whose RAS mutational status was evaluated and was found to be wild type.	

Primary: Overall response rate

End point title	Overall response rate
End point description:	
Complete response or partial response (modified RECIST)	
End point type	Primary
End point timeframe:	
From treatment start to the decision to end both treatments (Panitumumab and chemotherapy).	

End point values	Panitumumab + FOLFOX 4 (Safety Set)	Panitumumab + FOLFIRI (Safety Set)	Panitumumab + FOLFOX 4 (WT RAS Set)	Panitumumab + FOLFIRI (WT RAS Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	39	27	26
Units: percent				
number (confidence interval 95%)				
ORR (%)	74 (60 to 88)	67 (52 to 81)	78 (62 to 93)	73 (56 to 90)

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Panitumumab + FOLFIRI (Safety Set) v Panitumumab + FOLFOX 4 (Safety Set)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5012
Method	Chi-squared

Statistical analysis title	Chi-square test
Comparison groups	Panitumumab + FOLFOX 4 (WT RAS Set) v Panitumumab + FOLFIRI (WT RAS Set)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6909
Method	Chi-squared

Secondary: Hepatic resection rate

End point title	Hepatic resection rate

End point description:

Proportion of subjects with R0 (with tumour free margins and without evidence of microscopic and macroscopic residual disease) and R1 (microscopic residual margin) resections

End point type	Secondary

End point timeframe:

From treatment start to the decision to end both treatments (Panitumumab and chemotherapy).

End point values	Panitumumab + FOLFOX 4 (Safety Set)	Panitumumab + FOLFIRI (Safety Set)	Panitumumab + FOLFOX 4 (WT RAS Set)	Panitumumab + FOLFIRI (WT RAS Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	38	27	26
Units: percent				
number (confidence interval 95%)				
Rate (%)	34 (19 to 49)	46 (31 to 62)	26 (9 to 42)	54 (35 to 73)

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	Panitumumab + FOLFOX 4 (Safety Set) v Panitumumab + FOLFIRI (Safety Set)
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2853
Method	Fisher exact

Statistical analysis title	Fisher's exact test

Comparison groups	Panitumumab + FOLFOX 4 (WT RAS Set) v Panitumumab + FOLFIRI (WT RAS Set)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0378
Method	Fisher exact

Secondary: Time to resection

End point title	Time to resection

End point description:

Time to surgical resection in subjects who underwent metastatic surgery.

End point type	Secondary

End point timeframe:

From enrolment to the date of surgical resection.

End point values	Panitumumab + FOLFOX 4 (Safety Set)	Panitumumab + FOLFIRI (Safety Set)	Panitumumab + FOLFOX 4 (WT RAS Set)	Panitumumab + FOLFIRI (WT RAS Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	23	10	18
Units: months				
arithmetic mean (standard deviation)	5.0 (± 2.0)	5.5 (± 2.3)	5.4 (± 2.3)	5.5 (± 2.4)

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Panitumumab + FOLFOX 4 (Safety Set) v Panitumumab + FOLFIRI (Safety Set)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2832
Method	Logrank

Secondary: Duration of response

End point title	Duration of response

End point description:

End point type	Secondary

End point timeframe:

From first confirmed response to first observed disease progression or death (whichever came first).

End point values	Panitumumab + FOLFOX 4 (Safety Set)	Panitumumab + FOLFIRI (Safety Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	14		
Units: months				
median (inter-quartile range (Q1-Q3))	11 (5 to 22)	11 (6 to 16)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Panitumumab + FOLFOX 4 (Safety Set) v Panitumumab + FOLFIRI (Safety Set)
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7588
Method	Logrank

Secondary: Time to response

End point title	Time to response

End point description:

For subjects with a best response of stable disease, the date of their last evaluable radiographic assessment was recorded. For subjects with a best response of progressive disease, the date of their last evaluation was recorded.

End point type	Secondary

End point timeframe:

From treatment start to first confirmed complete response or partial response.

End point values	Panitumumab + FOLFOX 4 (Safety Set)	Panitumumab + FOLFIRI (Safety Set)	Panitumumab + FOLFOX 4 (WT RAS Set)	Panitumumab + FOLFIRI (WT RAS Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	36	27	26
Units: months				
arithmetic mean (standard error)	5.5 (± 0.3)	5.5 (± 0.6)	5.9 (± 0.3)	5.5 (± 0.3)

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Panitumumab + FOLFOX 4 (Safety Set) v Panitumumab + FOLFIRI (Safety Set)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.842
Method	Logrank

Statistical analysis title	Log-rank test
Comparison groups	Panitumumab + FOLFOX 4 (WT RAS Set) v Panitumumab + FOLFIRI (WT RAS Set)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9926
Method	Logrank

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

End point type	Secondary

End point timeframe:

From enrolment to treatment failure.

End point values	Panitumumab + FOLFOX 4 (Safety Set)	Panitumumab + FOLFIRI (Safety Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	39		
Units: months				
median (confidence interval 95%)	9 (5 to 11)	6 (5 to 15)		

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Panitumumab + FOLFOX 4 (Safety Set) v Panitumumab + FOLFIRI (Safety Set)

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7027
Method	Logrank

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Secondary

End point timeframe:

From treatment start to first observed disease progression or death (whichever came first).

End point values	Panitumumab + FOLFOX 4 (Safety Set)	Panitumumab + FOLFIRI (Safety Set)	Panitumumab + FOLFOX 4 (WT RAS Set)	Panitumumab + FOLFIRI (WT RAS Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	39	27	26
Units: months				
median (confidence interval 95%)	13 (6 to 15)	14 (7 to 16)	13 (6 to 19)	15 (7 to 19)

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Panitumumab + FOLFOX 4 (Safety Set) v Panitumumab + FOLFIRI (Safety Set)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7297
Method	Logrank

Statistical analysis title	Log-rank test
Comparison groups	Panitumumab + FOLFOX 4 (WT RAS Set) v Panitumumab + FOLFIRI (WT RAS Set)

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3047
Method	Logrank

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

From treatment start to death.

End point values	Panitumumab + FOLFOX 4 (Safety Set)	Panitumumab + FOLFIRI (Safety Set)	Panitumumab + FOLFOX 4 (WT RAS Set)	Panitumumab + FOLFIRI (WT RAS Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	39	27	26
Units: months				
median (confidence interval 95%)	37 (25 to 51)	41 (22 to 52)	39 (27 to 51)	49 (31 to 56)

Statistical analyses

Statistical analysis title	Log-rank test
Comparison groups	Panitumumab + FOLFOX 4 (Safety Set) v Panitumumab + FOLFIRI (Safety Set)
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9657
Method	Logrank

Statistical analysis title	Log-rank test
Comparison groups	Panitumumab + FOLFOX 4 (WT RAS Set) v Panitumumab + FOLFIRI (WT RAS Set)

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8237
Method	Logrank

Secondary: Depth of response

End point title	Depth of response

End point description:

Maximum tumour size decrease (%) with respect to baseline measurements (sum of lesion diameters) during treatment, prior to hepatic surgery.

End point type	Secondary

End point timeframe:

From treatment start to hepatic surgery.

End point values	Panitumumab + FOLFOX 4 (WT RAS Set)	Panitumumab + FOLFIRI (WT RAS Set)	All subjects (Safety Set)	All subjects (WT RAS Set)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	24	73	51
Units: percent				
median (inter-quartile range (Q1-Q3))	47 (32 to 71)	48 (42 to 64)	47 (32 to 60)	48 (32 to 67)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day -7 during the screening period to 30 ± 3 days after the end of study treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Panitumumab + FOLFOX 4

Reporting group description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and commencement of FOLFOX 4 chemotherapy. FOLFOX 4 was administered every 2 weeks (± 3 days) as follows:
Day 1: Oxaliplatin (85 mg/m2, intravenous infusion) and folinic acid (200 mg/m2, intravenous infusion), both given over 120 minutes (± 15 minutes) at the same time; followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2, intravenous infusion), given as a 22 hour (± 1 hour) continuous infusion.
Day 2: Folinic acid (200 mg/m2, intravenous infusion), given over 120 minutes (± 15 minutes); followed by 5-FU (400 mg/m2, intravenous bolus), given over 2 to 4 minutes; followed by 5-FU (600 mg/m2 intravenous infusion), given as a 22-hour (± 1 hour) continuous infusion.

Reporting group title	Panitumumab + FOLFIRI

Reporting group description:

Panitumumab was administered by intravenous infusion on day 1 of each cycle, just prior to administration of chemotherapy. A treatment cycle was defined as the 14 day period following treatment with panitumumab and FOLFIRI chemotherapy. FOLFIRI was administered every 2 weeks (± 3 days), on day 1 of each cycle, as follows: Irinotecan (180 mg/m2, intravenous infusion) was administered over 90 minutes ± 15 minutes. Folinic acid (400 mg/m2, intravenous infusion) was administered over 2 hours ± 15 minutes during irinotecan infusion. but without mixing. Immediately afterwards, a 5-FU intravenous bolus (400 mg/m2) was administered and a 5-FU intravenous infusion (2400 mg/m2) was given as 46-hour ± 2-hour continuous infusion.

Serious adverse events	Panitumumab + FOLFOX 4	Panitumumab + FOLFIRI	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 38 (34.21%)	15 / 39 (38.46%)	
number of deaths (all causes)	24	27	
number of deaths resulting from adverse events	2	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to peritoneum			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
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			
Anastomotic leak			

subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative fever			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (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 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	3 / 39 (7.69%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 38 (2.63%)	4 / 39 (10.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intra-abdominal fluid collection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal obstruction			

subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Pneumomediastinum			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (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	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	Panitumumab + FOLFOX 4	Panitumumab + FOLFIRI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 38 (100.00%)	39 / 39 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 38 (7.89%)	0 / 39 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 38 (65.79%)	24 / 39 (61.54%)	
occurrences (all)	43	52	
Chest pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Mucosal inflammation			
subjects affected / exposed	18 / 38 (47.37%)	22 / 39 (56.41%)	
occurrences (all)	45	34	
Pyrexia			
subjects affected / exposed	11 / 38 (28.95%)	7 / 39 (17.95%)	
occurrences (all)	14	11	
Xerosis			
subjects affected / exposed	3 / 38 (7.89%)	3 / 39 (7.69%)	
occurrences (all)	3	5	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	3 / 38 (7.89%)	0 / 39 (0.00%)	
occurrences (all)	5	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 38 (10.53%)	3 / 39 (7.69%)	
occurrences (all)	5	3	
Dyspnoea			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Epistaxis			

subjects affected / exposed	3 / 38 (7.89%)	1 / 39 (2.56%)	
occurrences (all)	6	1	
Hiccups			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	6	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	2	
Depression			
subjects affected / exposed	0 / 38 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Nail injury			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	8 / 38 (21.05%)	1 / 39 (2.56%)	
occurrences (all)	9	1	
Dysgeusia			
subjects affected / exposed	7 / 38 (18.42%)	5 / 39 (12.82%)	
occurrences (all)	7	7	

Headache			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Neurotoxicity			
subjects affected / exposed	20 / 38 (52.63%)	1 / 39 (2.56%)	
occurrences (all)	32	1	
Paraesthesia			
subjects affected / exposed	11 / 38 (28.95%)	2 / 39 (5.13%)	
occurrences (all)	14	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 38 (21.05%)	7 / 39 (17.95%)	
occurrences (all)	8	8	
Leukopenia			
subjects affected / exposed	4 / 38 (10.53%)	0 / 39 (0.00%)	
occurrences (all)	5	0	
Neutropenia			
subjects affected / exposed	24 / 38 (63.16%)	12 / 39 (30.77%)	
occurrences (all)	49	20	
Thrombocytopenia			
subjects affected / exposed	9 / 38 (23.68%)	1 / 39 (2.56%)	
occurrences (all)	16	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	7 / 38 (18.42%)	10 / 39 (25.64%)	
occurrences (all)	15	16	
Dry eye			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Trichomegaly			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	3	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	9 / 38 (23.68%)	2 / 39 (5.13%)	
occurrences (all)	15	5	
Abdominal pain upper			
subjects affected / exposed	1 / 38 (2.63%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
Anal fissure			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Cheilitis			
subjects affected / exposed	5 / 38 (13.16%)	0 / 39 (0.00%)	
occurrences (all)	9	0	
Constipation			
subjects affected / exposed	19 / 38 (50.00%)	15 / 39 (38.46%)	
occurrences (all)	39	22	
Diarrhoea			
subjects affected / exposed	29 / 38 (76.32%)	26 / 39 (66.67%)	
occurrences (all)	79	68	
Dry mouth			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Dyspepsia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Haematochezia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Haemorrhoids			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	15 / 38 (39.47%)	14 / 39 (35.90%)	
occurrences (all)	24	33	

Rectal haemorrhage			
subjects affected / exposed	3 / 38 (7.89%)	0 / 39 (0.00%)	
occurrences (all)	5	0	
Stomatitis			
subjects affected / exposed	2 / 38 (5.26%)	3 / 39 (7.69%)	
occurrences (all)	3	4	
Toothache			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	14 / 38 (36.84%)	10 / 39 (25.64%)	
occurrences (all)	24	33	
Proctalgia			
subjects affected / exposed	0 / 38 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	14 / 38 (36.84%)	5 / 39 (12.82%)	
occurrences (all)	29	11	
Alopecia			
subjects affected / exposed	2 / 38 (5.26%)	10 / 39 (25.64%)	
occurrences (all)	2	10	
Dermatitis			
subjects affected / exposed	6 / 38 (15.79%)	3 / 39 (7.69%)	
occurrences (all)	9	3	
Dermatitis acneiform			
subjects affected / exposed	5 / 38 (13.16%)	6 / 39 (15.38%)	
occurrences (all)	6	6	
Dry skin			
subjects affected / exposed	5 / 38 (13.16%)	3 / 39 (7.69%)	
occurrences (all)	7	4	
Erythema			
subjects affected / exposed	3 / 38 (7.89%)	3 / 39 (7.69%)	
occurrences (all)	3	6	
Hypertrichosis			

subjects affected / exposed	4 / 38 (10.53%)	1 / 39 (2.56%)	
occurrences (all)	6	1	
Nail disorder			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	3	
Nail toxicity			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 38 (7.89%)	4 / 39 (10.26%)	
occurrences (all)	3	7	
Pruritus			
subjects affected / exposed	6 / 38 (15.79%)	6 / 39 (15.38%)	
occurrences (all)	8	6	
Rash			
subjects affected / exposed	18 / 38 (47.37%)	26 / 39 (66.67%)	
occurrences (all)	36	41	
Skin fissures			
subjects affected / exposed	6 / 38 (15.79%)	3 / 39 (7.69%)	
occurrences (all)	6	3	
Skin toxicity			
subjects affected / exposed	2 / 38 (5.26%)	2 / 39 (5.13%)	
occurrences (all)	2	3	
Telangiectasia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Toxic skin eruption			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	4	1	
Xeroderma			
subjects affected / exposed	0 / 38 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Dysuria			

subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 38 (7.89%)	1 / 39 (2.56%)	
occurrences (all)	4	1	
Back pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
Myalgia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Infections and infestations			
Device related infection			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Folliculitis			
subjects affected / exposed	2 / 38 (5.26%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	1 / 38 (2.63%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
Paronychia			
subjects affected / exposed	11 / 38 (28.95%)	11 / 39 (28.21%)	
occurrences (all)	22	14	
Urinary tract infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 38 (21.05%)	11 / 39 (28.21%)	
occurrences (all)	14	16	
Hyperglycaemia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Hypomagnesaemia			

subjects affected / exposed	9 / 38 (23.68%)	12 / 39 (30.77%)	
occurrences (all)	14	15	
Hypoproteinaemia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 39 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2008	Removal of "Administrative decision by the study sponsor" as a reason for withdrawal of patients from study treatment or from observation. In conjunction with this Amendment, the Patient Information Sheet and Informed Consent Form were updated. Notably, a Patient Information Sheet was created for the optional new marker study. These changes were made in response to feedback from the Independent Ethics Committees involved in this study.
03 March 2009	Update to the Patient Information Sheet based on new information regarding the administration/safety of one of the study treatments (Panitumumab).
15 March 2010	Addition of 2 new secondary objectives: (1) to assess the effects of the study treatments in terms of overall survival and (2) to assess hypomagnesaemia as a predictor of response to study treatment. Modification of the study endpoints to reflect the changes in the secondary objectives. Change of definition of the adjuvant treatment regimen to 12 complete cycles (including neoadjuvant treatment cycles received before surgery) of the allocated study treatment regimen. Correction of error in age of subjects eligible for enrollment. Inclusion criteria: metastases permitted to be resectable or non-resectable (not only non-resectable). Clarification of the definition of delay to surgery due to study treatment-related toxicity. Definition of end of study modified. Specification of version of RECIST to be used. Information regarding storage and handling of Panitumumab updated. Amendment/updating of the objectives of the parallel study of genetic factors.
24 November 2010	Inclusion criteria/screening procedures: removal of the requirement for KRAS gene analysis to be performed by the designated central laboratory (thus permitting it to be performed locally). The reason for this was minimize the delay in starting treatment in eligible patients, since Spanish hospitals perform a KRAS analysis as part of routine clinical practice in patients with metastatic colorectal cancer.
28 February 2011	Update to the "SAFETY - POTENTIAL RISKS AND DISCOMFORT" section of the Patient Information Sheet based on new information regarding the safety of combination treatment with Panitumumab plus chemotherapy.
15 May 2013	Change of Principal Investigator at 2 of the study sites. Creation of an addendum to the Patient Information Sheet detailing new safety information, which all patients included in the study were required to sign. This was because the phase III PRIME (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy) study had shown that patients with RAS mutations in regions other than codon 2 who received Panitumumab plus FOLFOX had lower progression-free survival and overall survival compared to patients treated with FOLFOX alone.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported