



Clinical trial results:

An open-label 2:1 randomized phase II study of panitumumab plus FOLFOXIRI or FOLFOXIRI alone as first-line treatment of patients with non-resectable metastatic colorectal cancer and RAS wild-type

Summary

EudraCT number	2009-017731-17
Trial protocol	DE
Global end of trial date	20 January 2022

Results information

Result version number	v1 (current)
This version publication date	29 October 2023
First version publication date	29 October 2023

Trial information

Trial identification

Sponsor protocol code	AIO-KRK-0109
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01328171
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIO-Studien-gGmbH
Sponsor organisation address	Kuno-Fischer-Str. 8, Berlin, Germany, 14057
Public contact	info@aio-studien-ggmbh.de, AIO-Studien-gGmbH, info@aio-studien-ggmbh.de
Scientific contact	info@aio-studien-ggmbh.de, AIO-Studien-gGmbH, info@aio-studien-ggmbh.de

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	07 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2017
Global end of trial reached?	Yes
Global end of trial date	20 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy (objective response rate, ORR) of adding panitumumab to FOLFOXIRI in patients with newly diagnosed metastatic colorectal cancer expressing wild-type RAS

Cohort I) With definitively unresectable metastatic disease, with a focus on symptomatic metastatic disease and/or large tumor load,

or

Cohort II) With chance of secondary resection with curative intent according to recent S3 guidelines of the German Cancer Society. The ORR was to be compared to expectations derived from historical data, which are verified by a randomised control group without the antibody.

Protection of trial subjects:

This study was planned, analyzed and conducted according to the study protocol and in accordance with the International Conference on Harmonization (ICH) 'Guideline for Good Clinical Practice E6(R1)', CPMP/ICH/135/95, based on the principles of the Declaration of Helsinki (1964) and its October 1996 amendment (Somerset West, South Africa). The study was duly conducted in compliance with the German Arzneimittelgesetz (AMG; German Drug Law), and the corresponding Directive 2001/20/EC. Subjects were fully informed regarding all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 102
Worldwide total number of subjects	102
EEA total number of subjects	102

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)	79
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 105 patients were randomised into the clinical trial, 71 to receive FOLFOXIRI + Panitumumab (Arm A), and 34 to receive FOLFOXIRI alone (Arm B). 102 patients received at least one dose of randomised therapy with FOLFOXIRI + panitumumab or FOLFOXIRI alone.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FOLFOXIRI + Panitumumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Panitumumab was given at 6 mg/kg Q2W for a maximum of 12 cycles, or until disease progression, unacceptable toxicity, treatment delay of more than 3 weeks, withdrawal of consent, or death.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU was given at 3000 mg/m² body surface Q2W, for a maximum of 12 cycles, or until disease progression, unacceptable toxicity, treatment delay of more than 3 weeks, withdrawal of consent, or death.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin was given at 85 mg/m² body surface area, Q2W, for a maximum of 12 cycles, or until disease progression, unacceptable toxicity, treatment delay of more than 3 weeks, withdrawal of consent, or death.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan was given at 150 mg/m² body surface area, Q2W, for a maximum of 12 cycles, or until disease progression, unacceptable toxicity, treatment delay of more than 3 weeks, withdrawal of consent, or death.

Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Folinic acid was given at 200 mg/m² body surface area, Q2W, for a maximum of 12 cycles, or until disease progression, unacceptable toxicity, treatment delay of more than 3 weeks, withdrawal of consent, or death.

Arm title	FOLFOXIRI
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU was given at 3000 mg/m² body surface area Q2W, for a maximum of 12 cycles, or until disease progression, unacceptable toxicity, treatment delay of more than 3 weeks, withdrawal of consent, or death.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin was given at 85 mg/m² body surface area, Q2W, for a maximum of 12 cycles, or until disease progression, unacceptable toxicity, treatment delay of more than 3 weeks, withdrawal of consent, or death.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan was given at 150 mg/m² body surface area, Q2W, for a maximum of 12 cycles, or until disease progression, unacceptable toxicity, treatment delay of more than 3 weeks, withdrawal of consent, or death.

Number of subjects in period 1	FOLFOXIRI + Panitumumab	FOLFOXIRI
Started	68	34
Completed	68	34

Baseline characteristics

Reporting groups

Reporting group title	FOLFOXIRI + Panitumumab
Reporting group description: -	
Reporting group title	FOLFOXIRI
Reporting group description: -	

Reporting group values	FOLFOXIRI + Panitumumab	FOLFOXIRI	Total
Number of subjects	68	34	102
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	55	24	79
From 65-84 years	13	10	23
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	22	9	31
Male	46	25	71
ECOG			
Units: Subjects			
ECOG 0	40	21	61
ECOG 1	27	12	39
ECOG 2	1	1	2

End points

End points reporting groups

Reporting group title	FOLFOXIRI + Panitumumab
Reporting group description: -	
Reporting group title	FOLFOXIRI
Reporting group description: -	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description:	ORR was defined as the proportion of patients of the FAS with CR or PR according to RECIST 1.1 criteria as best response
End point type	Primary
End point timeframe:	Only restagings during study treatment or until 30 days after the administration of the last dose of any substance but before any tumour resection or other new anticancer therapy (further treatment line and/or radiotherapy) were considered in the analyses

End point values	FOLFOXIRI + Panitumumab	FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	33		
Units: Patients with CR or PR	55	20		

Statistical analyses

Statistical analysis title	Statistical analysis primary endpoint - ORR
Comparison groups	FOLFOXIRI + Panitumumab v FOLFOXIRI
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.0041
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	4.469
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.614
upper limit	12.376

Notes:

[1] - All parameters were evaluated in an explorative or descriptive manner. This includes any p values that were calculated.

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
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End point description:

Disease Control Rate (DCR) was defined as the proportion of patients with CR, PR, or stable disease (SD) according to RECIST 1.1 criteria as best response.

End point type	Secondary
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End point timeframe:

See primary endpoint

End point values	FOLFOXIRI + Panitumumab	FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	33		
Units: Patients with CR, PR or SD	60	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Resection Rate - all patients

End point title	Secondary Resection Rate - all patients
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End point description:

A higher percentage of patients achieved resectability in the FOLFOXIRI + panitumumab arm (21 of 63 patients; 33.3%) than in the FOLFOXIRI arm (5 of 33 patients; 15.2%), but this result was not statistically significant (OR 2.800 [0.945–8.297]; p-value 0.0893). In cohort I, at least 6 of 43 patients of arm A (14.0%) and none of the patients of arm B were resectable. As was to be expected, the rates were much higher in cohort II, with 15 of 20 patients of arm A (75.0%) and 5 of 11 patients of arm B (45.5%) achieving resectability. Again, in both cohorts, the results in favour of FOLFOXIRI + panitumumab were not statistically significant (Fisher's exact test p-values 0.0884 and 0.1318, respectively)

End point type	Secondary
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End point timeframe:

Secondary resection rate was calculated for for all patients, and for a cohort (cohort II) with chance of secondary resection with curative intent at study enrollment.

End point values	FOLFOXIRI + Panitumumab	FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	33		
Units: Patients with 2° resection	21	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival
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End point description:

For patients without either of these events (progression/relapse, or death), the PFS time was censored at the date of the patient's last recorded date without event. The median duration of observation (time from randomisation to last contact / death) was 32.7 months (mean $\pm$ SD: 35.4 $\pm$ 26.1 months, minimum 0.8, maximum 124.0 months).

End point type	Secondary
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End point timeframe:

Progression-free survival (PFS) was the time from the date of randomisation to the date of disease progression or relapse (according to RECIST 1.1) or death of any cause, whichever occurred first.

End point values	FOLFOXIRI + Panitumumab	FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	33		
Units: Months				
median (confidence interval 95%)	10.3 (8.7 to 11.8)	10.5 (9.0 to 13.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
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End point description:

End point type	Secondary
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End point timeframe:

Overall survival (OS) was the time from the date of randomisation to the date of death of any cause. For patients without event (death), the OS time was censored at the date of the patient's last recorded observation.

End point values	FOLFOXIRI + Panitumumab	FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	33		
Units: Months				
median (confidence interval 95%)	33.7 (24.7 to 42.8)	29.8 (16.6 to 39.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
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End point description:

Only responders were included in this analysis. For patients without progression or death, the DOR time was censored at the patient's last recorded progression-free date.

End point type	Secondary
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End point timeframe:

Duration of response (DOR) was calculated as the time from first reaching response (CR or PR) until first progression or death.

End point values	FOLFOXIRI + Panitumumab	FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	20		
Units: Months				
median (confidence interval 95%)	8.8 (7.0 to 9.9)	10.3 (8.0 to 26.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response

End point title	Time to response
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End point description:

For patients without either CR or PR, TTR time was censored at the patient's last administration of any substance (irinotecan, oxaliplatin, 5-FU, folinic acid, or panitumumab) during study treatment.

End point type	Secondary
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End point timeframe:

Time to response (TTR) was calculated as the time from randomisation until first observation of response (CR or PR).

End point values	FOLFOXIRI + Panitumumab	FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	33		
Units: Months				
median (confidence interval 95%)	2.0 (1.8 to 2.1)	4.9 (2.6 to 6.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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Reporting groups

Reporting group title	FOLFOXIRI + Panitumumab
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Reporting group description: -

Reporting group title	FOLFOXIRI
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Reporting group description: -

Serious adverse events	FOLFOXIRI + Panitumumab	FOLFOXIRI	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 68 (51.47%)	16 / 34 (47.06%)	
number of deaths (all causes)	68	34	
number of deaths resulting from adverse events	1	2	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 68 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 68 (1.47%)	3 / 34 (8.82%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Benign prostatic hyperplasia subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung infiltration subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism subjects affected / exposed	2 / 68 (2.94%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Blood creatine increased subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arterial restenosis			

subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular bypass dysfunction			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arteriospasm coronary			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholinergic syndrome			

subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope0			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 68 (2.94%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 68 (4.41%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	10 / 68 (14.71%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	13 / 13	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glossitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	4 / 68 (5.88%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal stenosis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	2 / 68 (2.94%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 68 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin toxicity			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 68 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (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 infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 68 (1.47%) 1 / 1 0 / 0	 0 / 34 (0.00%) 0 / 0 0 / 0	
Biliary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 68 (0.00%) 0 / 0 0 / 0	 1 / 34 (2.94%) 0 / 1 0 / 0	
Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 68 (0.00%) 0 / 0 0 / 0	 1 / 34 (2.94%) 0 / 1 0 / 0	
Clostridium difficile infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 68 (1.47%) 1 / 1 0 / 0	 0 / 34 (0.00%) 0 / 0 0 / 0	
Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 2 / 68 (2.94%) 0 / 2 0 / 0	 0 / 34 (0.00%) 0 / 0 0 / 0	
Escherichia infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 68 (0.00%) 0 / 0 0 / 0	 1 / 34 (2.94%) 0 / 1 0 / 0	
Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 2 / 68 (2.94%) 2 / 3 0 / 0	 0 / 34 (0.00%) 0 / 0 0 / 0	
Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 68 (1.47%) 1 / 1 0 / 0	 1 / 34 (2.94%) 0 / 1 0 / 0	
Neutropenic infection			

subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incorrect drug administration rate			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 68 (2.94%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			

subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 68 (1.47%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FOLFOXIRI + Panitumumab	FOLFOXIRI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 68 (98.53%)	34 / 34 (100.00%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 68 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	3	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 68 (10.29%)	0 / 34 (0.00%)	
occurrences (all)	22	0	
Weight decreased			
subjects affected / exposed	6 / 68 (8.82%)	1 / 34 (2.94%)	
occurrences (all)	14	2	
Vascular disorders			
Hypertension			

subjects affected / exposed	4 / 68 (5.88%)	6 / 34 (17.65%)	
occurrences (all)	10	15	
Hypotension			
subjects affected / exposed	4 / 68 (5.88%)	3 / 34 (8.82%)	
occurrences (all)	6	3	
Peripheral coldness			
subjects affected / exposed	1 / 68 (1.47%)	2 / 34 (5.88%)	
occurrences (all)	1	5	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	5 / 68 (7.35%)	0 / 34 (0.00%)	
occurrences (all)	8	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 68 (7.35%)	1 / 34 (2.94%)	
occurrences (all)	10	5	
Dysgeusia			
subjects affected / exposed	13 / 68 (19.12%)	4 / 34 (11.76%)	
occurrences (all)	24	5	
Neuropathy peripheral			
subjects affected / exposed	44 / 68 (64.71%)	23 / 34 (67.65%)	
occurrences (all)	169	83	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 68 (17.65%)	5 / 34 (14.71%)	
occurrences (all)	35	13	
Leukopenia			
subjects affected / exposed	16 / 68 (23.53%)	11 / 34 (32.35%)	
occurrences (all)	41	14	
Neutropenia			
subjects affected / exposed	15 / 68 (22.06%)	12 / 34 (35.29%)	
occurrences (all)	41	18	
Thrombocytopenia			
subjects affected / exposed	4 / 68 (5.88%)	6 / 34 (17.65%)	
occurrences (all)	7	13	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	44 / 68 (64.71%)	22 / 34 (64.71%)	
occurrences (all)	158	64	
Oedema peripheral			
subjects affected / exposed	4 / 68 (5.88%)	3 / 34 (8.82%)	
occurrences (all)	5	6	
Pain			
subjects affected / exposed	26 / 68 (38.24%)	15 / 34 (44.12%)	
occurrences (all)	50	44	
Pyrexia			
subjects affected / exposed	7 / 68 (10.29%)	3 / 34 (8.82%)	
occurrences (all)	8	3	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	4 / 68 (5.88%)	2 / 34 (5.88%)	
occurrences (all)	6	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 68 (5.88%)	2 / 34 (5.88%)	
occurrences (all)	17	3	
Diarrhoea			
subjects affected / exposed	46 / 68 (67.65%)	24 / 34 (70.59%)	
occurrences (all)	143	69	
Dyspepsia			
subjects affected / exposed	2 / 68 (2.94%)	4 / 34 (11.76%)	
occurrences (all)	2	6	
Nausea			
subjects affected / exposed	39 / 68 (57.35%)	23 / 34 (67.65%)	
occurrences (all)	93	74	
Stomatitis			
subjects affected / exposed	40 / 68 (58.82%)	13 / 34 (38.24%)	
occurrences (all)	138	28	
Vomiting			
subjects affected / exposed	24 / 68 (35.29%)	10 / 34 (29.41%)	
occurrences (all)	45	15	
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	9 / 68 (13.24%)	2 / 34 (5.88%)	
occurrences (all)	15	8	
Rhinorrhoea			
subjects affected / exposed	1 / 68 (1.47%)	3 / 34 (8.82%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	25 / 68 (36.76%)	13 / 34 (38.24%)	
occurrences (all)	100	45	
Dermatitis			
subjects affected / exposed	6 / 68 (8.82%)	0 / 34 (0.00%)	
occurrences (all)	43	0	
Dermatitis acneiform			
subjects affected / exposed	42 / 68 (61.76%)	0 / 34 (0.00%)	
occurrences (all)	164	0	
Dry skin			
subjects affected / exposed	37 / 68 (54.41%)	10 / 34 (29.41%)	
occurrences (all)	127	24	
Exfoliative rash			
subjects affected / exposed	24 / 68 (35.29%)	1 / 34 (2.94%)	
occurrences (all)	77	1	
Hyperhidrosis			
subjects affected / exposed	2 / 68 (2.94%)	2 / 34 (5.88%)	
occurrences (all)	2	8	
Nail disorder			
subjects affected / exposed	9 / 68 (13.24%)	1 / 34 (2.94%)	
occurrences (all)	14	2	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	20 / 68 (29.41%)	5 / 34 (14.71%)	
occurrences (all)	44	9	
Pruritus			
subjects affected / exposed	12 / 68 (17.65%)	0 / 34 (0.00%)	
occurrences (all)	39	0	
Infections and infestations			

Conjunctivitis subjects affected / exposed occurrences (all)	7 / 68 (10.29%) 16	1 / 34 (2.94%) 2	
Infection subjects affected / exposed occurrences (all)	21 / 68 (30.88%) 43	9 / 34 (26.47%) 21	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	10 / 68 (14.71%) 16	4 / 34 (11.76%) 5	
Hypocalcaemia subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 10	0 / 34 (0.00%) 0	
Hypokalaemia subjects affected / exposed occurrences (all)	15 / 68 (22.06%) 32	4 / 34 (11.76%) 6	
Hypomagnesaemia subjects affected / exposed occurrences (all)	12 / 68 (17.65%) 54	2 / 34 (5.88%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2011	- Implementation of local KRAS mutation testing - Exclusion of patients with baseline ECOG > 1
20 November 2011	- o Introduction of a possible FOLFOXIRI pre-cycle in patients waiting for their RAS mutation test result in need of immediate treatment - o In an immediate measure of 28 October 2011, after receipt of safety information from another trial with FOLFOXIRI + panitumumab in mCRC, the doses of irinotecan and 5-FU in the experimental arm had been reduced (irinotecan: 165 mg/m² to 130 mg/m²; 5-FU 3200 mg/m² to 2400 mg/m²); in consultation with the IDMC, irinotecan 150 mg/m² and 5-FU 3000 mg/m² were determined as the start doses in the FOLFOXIRI + panitumumab arm. - o Closer safety monitoring because of the risk of severe toxicities and early life-threatening adverse reactions during the first 4 weeks of treatment for early identification of risk patients in order to take prophylactic / preventive measures. - o Implementation of a formal interim analysis
20 November 2013	- o The Contract Research Organisation supporting the trial was changed in September 2013, when ClinAssess took over the services from the previously contracted CRO. This resulted in numerous organisational and administrative changes, including new randomisation, safety reporting, and data management contact points, procedures, and systems. - o After receipt of overall survival (OS) and progression-free survival (PFS) data from a clinical trial with panitumumab + FOLFOX showing NRAS and KRAS Exon 2-4 mutations as a significant negative predictive marker for panitumumab + FOLFOX therapy, mandatory RAS mutation testings prior to patient inclusion and restriction of participation to RAS wildtype patients had already been implemented on 24 April 2013 to prevent any harm to patients; moreover, all patients already included had to be tested. In amendment 3, this measure was laid down in the protocol. - o As all patients irrespective of their randomisation to the experimental FOLFOXIRI + Panitumumab arm or the standard FOLFOXIRI (alone) arm received 5-FU / folinic acid, oxaliplatin, and irinotecan, FOLFOXIRI had to be considered background medication and panitumumab was the only investigational medicinal product (IMP) of the study.
29 September 2014	- o Response (CR / PR) did no longer need to be confirmed in a subsequent response assessment (CR / PR) no less than 4 weeks after the initial response assessment, because this condition did not represent the clinical reality in this specific patient population - o Examinations / restagings in patients being administered a FOLFOXIRI pre-cycle as implemented in amendment 2 were rescheduled.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32449003>

<http://www.ncbi.nlm.nih.gov/pubmed/31609637>