Clinical trial results:
Randomisierte Studie zur Wirksamkeit von FOLFIRI in Kombination mit Cetuximab vs. Bevacizumab in der Erstlinien-Behandlung des metastasierten kolorektalen Karzinoms

English translation:
Randomised study for efficiency of FOLFIRI in combination with Cetuximab vs. Bevacizumab in first-line-therapy of metastatic colorectal cancer

Summary

EudraCT number	2006-004030-32
Trial protocol	DE AT
Global end of trial date	21 November 2017

Results information

Result version number	v1 (current)
This version publication date	29 September 2021
First version publication date	29 September 2021
Summary attachment (see zip file)	Final Report ACCORDING TO § 42B (2) German Drug Law (Fire3_CSR_Version_2.0_30-Jul-2019.pdf)

Trial information

Trial identification

Sponsor protocol code	AIOKRK0306

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Klinikum der Universität München - Grosshadern
Sponsor organisation address	Marchioninistraße 15, München, Germany, 81377
Public contact	Medizinische Klinik III AG Onkologie, Klinikum der Universität München - Grosshadern, +49 89 4400 0, onkologiestudien@med.uni-muenchen.de
Scientific contact	Medizinische Klinik III AG Onkologie, Klinikum der Universität München - Grosshadern, +49 89 4400 0, onkologiestudien@med.uni-muenchen.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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	30 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2017
Global end of trial reached?	Yes
Global end of trial date	21 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Comparative validation of antitumor efficacy measured by objective remissionrate defined by RECIST-criteria (OR= CR+ PR), assessed within intent-to-treat-collective.

Protection of trial subjects:

All adverse events (AEs) for each cycle were recorded from the first day of administration of study medication until the end of treatment. Adverse events, denoted as late toxicities were also recorded every
three months during follow up.
Signs, symptoms or medical conditions/diseases that were already present before a subject obtained study drug treatment were only recorded as AEs if they worsened during study treatment.
There were 27 preprinted terms for common adverse events that could be ticked off in each treatment cycle
with space to fill in other adverse events than those recorded with the preprinted terms. Other adverse events were coded by MedDRA preferred terms and assigned to the preprinted terms if appropriate. The severity of AEs had to be graded according to the NCI CTCAE version 3.0 whenever possible and the causal relationship to the investigational drugs to be evaluated. An AE was analysed as causally related to
study medication when the AE was evaluated by the investigator as causally related to at least one of the
investigational drugs (5-FU, folinic acid, irinotecan, cetuximab, bevacizumab) administered in the respective
treatment arm.
All recorded adverse events were summarized in frequency counts based on the preprinted terms and MedDRA preferred terms assigned to other adverse events on patient level. A preprinted term or preferred
term was counted only once per patient. A patient with several grades of a preferred term was counted once with the highest NCI-CTCAE grade.
In addition, the data of laboratory investigations were analysed.
Data from all patients who received at least one dose of any study drug were included in the safety analyses.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 35
Country: Number of subjects enrolled	Germany: 717
Worldwide total number of subjects	752
EEA total number of subjects	752

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)	559
From 65 to 84 years	193
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	752
Number of subjects completed	752

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	FOLFIRI + Cet

Arm description:

1 cycle consisting of:
• FOLFIRI regimen, every 2 weeks

Irinotecan 180 mg/m² i.v., 30 - 90 min	day 1
Folinic acid (racemic) 400 mg/m² i.v., 120 min	day 1
5-FU 400 mg/m² bolus	day 1
5-FU 2400 mg/m² i.v. over a period of 46 h	day 1-2
Cetuximab initially 400mg/m² as 120-min infusion, followed by 250 mg/m² i.v. as 60-min infusion each	day 1 + 8

Arm type	Experimental
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

180 mg/m² i.v., 30 - 90 min day 1

Investigational medicinal product name	Folinic acid (racemic)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Folinic acid (racemic) 400 mg/m² i.v., 120 min day 1

Investigational medicinal product name	5-FU bolus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

400 mg/m² bolus day 1

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

5-FU 2400 mg/m² i.v. over a period of 46 h day 1-2

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Cetuximab initially 400mg/m² as 120-min infusion, followed by 250 mg/m² i.v. as 60-min infusion each day 1 + 8

Arm title	FOLFIRI + Bev

Arm description:

1 cycle consisting of:
• FOLFIRI regimen, every 2 weeks

Irinotecan 180 mg/m² i.v., 30 - 90 min	day 1
Folinic acid (racemic) 400 mg/m² i.v., 120 min	day 1
5-FU 400 mg/m² bolus	day 1
5-FU 2400 mg/m² i.v. over a period of 46 h	day 1-2
Bevacizumab 5 mg/kg of BW i.v. for 30 to 90* minutes	day 1

* The 1st administration is given over a period of 90 min, if tolerated well, the second administration over a period of 60 min and the further administrations over a period of 30 min each

Continuation of the treatment until:

• the tumor progresses
• inacceptable toxicity is observed
• confirmed CR is achieved
• a status for surgical treatment is achieved
• the patient asks to end the treatment
• the treating physician decides that the therapy should be withdrawn

Arm type	Active comparator
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

180 mg/m² i.v., 30 - 90 min day 1

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

180 mg/m² i.v., 30 - 90 min day 1

Investigational medicinal product name	Folinic acid (racemic)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Infusion
Dosage and administration details: Folinic acid (racemic) 400 mg/m² i.v., 120 min day 1	
Investigational medicinal product name	5-FU bolus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection
Dosage and administration details: 400 mg/m² bolus day 1	
Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion
Dosage and administration details: 5-FU 2400 mg/m² i.v. over a period of 46 h day 1-2	
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion
Dosage and administration details: Bevacizumab 5 mg/kg of BW i.v. for 30 to 90* minutes day 1	

Number of subjects in period 1	FOLFIRI + Cet	FOLFIRI + Bev
Started	380	372
Completed	380	372

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	752	752	
Age categorical Units: Subjects			
Adults (18-64 years)	559	559	
From 65-84 years	193	193	
Not recorded	0	0	
Age continuous Units: years			
median	64		
full range (min-max)	27 to 79	-	
Gender categorical Units: Subjects			
Female	240	240	
Male	509	509	
unknown	3	3	
KRAS Status Units: Subjects			
KRAS wild-typ	593	593	
KRAS mutation	113	113	
Not recorded	46	46	
ECOG Performance status Units: Subjects			
ECOG 0	394	394	
ECOG 1	340	340	
ECOG 2	18	18	
Not recorded	0	0	

End points

End points reporting groups

Reporting group title	FOLFIRI + Cet

Reporting group description:

1 cycle consisting of:
• FOLFIRI regimen, every 2 weeks

Irinotecan 180 mg/m² i.v., 30 - 90 min	day 1
Folinic acid (racemic) 400 mg/m² i.v., 120 min	day 1
5-FU 400 mg/m² bolus	day 1
5-FU 2400 mg/m² i.v. over a period of 46 h	day 1-2
Cetuximab initially 400mg/m² as 120-min infusion, followed by 250 mg/m² i.v. as 60-min infusion each	day 1 + 8

Reporting group title	FOLFIRI + Bev

Reporting group description:

1 cycle consisting of:
• FOLFIRI regimen, every 2 weeks

Irinotecan 180 mg/m² i.v., 30 - 90 min	day 1
Folinic acid (racemic) 400 mg/m² i.v., 120 min	day 1
5-FU 400 mg/m² bolus	day 1
5-FU 2400 mg/m² i.v. over a period of 46 h	day 1-2
Bevacizumab 5 mg/kg of BW i.v. for 30 to 90* minutes	day 1

* The 1st administration is given over a period of 90 min, if tolerated well, the second administration over a period of 60 min and the further administrations over a period of 30 min each

Continuation of the treatment until:

• the tumor progresses
• inacceptable toxicity is observed
• confirmed CR is achieved
• a status for surgical treatment is achieved
• the patient asks to end the treatment
• the treating physician decides that the therapy should be withdrawn

Primary: objective response rate (ORR)

End point title	objective response rate (ORR)

End point description:

End point type	Primary

End point timeframe:

the number of patients with either complete (CR) or partial response (PR) relative to the total number of subjects in the study population of interest. Only the results from restaging examinations during study therapy and until 28 days after the end.

End point values	FOLFIRI + Cet	FOLFIRI + Bev		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	295		
Units: percent				
number (confidence interval 95%)	62.1 (56.3 to 67.6)	58.3 (52.4 to 64.0)		

Statistical analyses

Statistical analysis title	Efficacy Results to SAF Dataset
Statistical analysis description:	
1-sided Fisher's exact test and alpha = 0.025	
Comparison groups	FOLFIRI + Cet v FOLFIRI + Bev
Number of subjects included in analysis	593
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.192 [1]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.63
Variability estimate	Standard error of the mean

Notes:

[1] - Thus, the primary endpoint was not reached and the ORR was not improved in patients treated with
FOLFIRI plus cetuximab.

Secondary: progression free survival (PFS)

End point title	progression free survival (PFS)
End point description:	
End point type	Secondary

End point timeframe:

PFS was defined as the time from randomisation until first occurrence of PD or death, whichever occurred
first. Subjects alive and without progression at the last date of assessment were censored.

End point values	FOLFIRI + Cet	FOLFIRI + Bev		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: months				
median (confidence interval 95%)				
PFS	10.1 (8.7 to 10.9)	10.5 (9.9 to 11.5)		

Statistical analyses

Statistical analysis title	KRAS-wild-type patients, SAF
Comparison groups	FOLFIRI + Cet v FOLFIRI + Bev
Number of subjects included in analysis	400
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.46
Method	Fisher exact
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.26
Variability estimate	Standard deviation

Secondary: overall survival	
End point title	overall survival

End point description:

End point type	Secondary

End point timeframe:

OS was defined as the time from randomisation to the date of death of any cause. Subjects who were alive
at the date of the last assessment were censored.

End point values	FOLFIRI + Cet	FOLFIRI + Bev		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: months				
median (confidence interval 95%)				
OS	27.9 (23.7 to 31.7)	25.6 (23.2 to 28.2)		

Statistical analyses

Statistical analysis title	KRAS-wild-type patients, SAF
Comparison groups	FOLFIRI + Cet v FOLFIRI + Bev
Number of subjects included in analysis	400
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.05
Method	Fisher exact
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.706
upper limit	1.001
Variability estimate	Standard deviation

Secondary: Time to failure of strategy of the first-line treatment

End point title	Time to failure of strategy of the first-line treatment

End point description:

End point type	Secondary

End point timeframe:

TFS was defined as the duration from randomisation to the date of death or start of a new systemic anticancer therapy that contained a substance not included in the study therapy (start of second-line therapy).

End point values	FOLFIRI + Cet	FOLFIRI + Bev		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: months				
median (confidence interval 95%)				
TFS	11.4 (10.1 to 12.6)	12.1 (11.1 to 13.1)		

Statistical analyses

Statistical analysis title	Time to failure of strategy of the first-line trea
Comparison groups	FOLFIRI + Cet v FOLFIRI + Bev

Number of subjects included in analysis	400
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.42
Method	Fisher exact
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.27
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) for each cycle were recorded from the first day of administration of study medication until the end of treatment. Adverse events, denoted as late toxicities were also recorded every
three months during follow up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	adverse events according to SAF

Reporting group description: -

Serious adverse events	adverse events according to SAF		
Total subjects affected by serious adverse events			
subjects affected / exposed	252 / 734 (34.33%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	13		
Injury, poisoning and procedural complications			
Bone fracture			
subjects affected / exposed	3 / 734 (0.41%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	6 / 734 (0.82%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Cardiac disorder			
subjects affected / exposed	10 / 734 (1.36%)		
occurrences causally related to treatment / all	4 / 10		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Pain			

subjects affected / exposed	26 / 734 (3.54%)		
occurrences causally related to treatment / all	3 / 26		
deaths causally related to treatment / all	0 / 0		
handfoot syndrom			
subjects affected / exposed	1 / 734 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neurotoxicity			
subjects affected / exposed	3 / 734 (0.41%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thromboembolic event			
subjects affected / exposed	66 / 734 (8.99%)		
occurrences causally related to treatment / all	25 / 66		
deaths causally related to treatment / all	0 / 1		
Haematotoxicity			
subjects affected / exposed	10 / 734 (1.36%)		
occurrences causally related to treatment / all	8 / 10		
deaths causally related to treatment / all	0 / 0		
Bleeding			
subjects affected / exposed	2 / 734 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Edema peripheral			
subjects affected / exposed	3 / 734 (0.41%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Endocrine disorder			
subjects affected / exposed	1 / 734 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Fatigue				
subjects affected / exposed	4 / 734 (0.54%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	3 / 734 (0.41%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Mucositis				
subjects affected / exposed	6 / 734 (0.82%)			
occurrences causally related to treatment / all	5 / 6			
deaths causally related to treatment / all	1 / 1			
Nail changes				
subjects affected / exposed	2 / 734 (0.27%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
other				
subjects affected / exposed	54 / 734 (7.36%)			
occurrences causally related to treatment / all	15 / 54			
deaths causally related to treatment / all	1 / 6			
Psychiatric disorder				
subjects affected / exposed	4 / 734 (0.54%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Fever without neutropenia				
subjects affected / exposed	20 / 734 (2.72%)			
occurrences causally related to treatment / all	6 / 20			
deaths causally related to treatment / all	0 / 0			
Allergic reaction				
subjects affected / exposed	11 / 734 (1.50%)			
occurrences causally related to treatment / all	11 / 11			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				

subjects affected / exposed	7 / 734 (0.95%)		
occurrences causally related to treatment / all	2 / 7		
deaths causally related to treatment / all	0 / 0		
Fever with neutropenia			
subjects affected / exposed	4 / 734 (0.54%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	40 / 734 (5.45%)		
occurrences causally related to treatment / all	38 / 40		
deaths causally related to treatment / all	0 / 0		
Bleeding respected to GI tract			
subjects affected / exposed	11 / 734 (1.50%)		
occurrences causally related to treatment / all	6 / 11		
deaths causally related to treatment / all	1 / 1		
fistula perforation			
subjects affected / exposed	6 / 734 (0.82%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	5 / 734 (0.68%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Obstipation			
subjects affected / exposed	8 / 734 (1.09%)		
occurrences causally related to treatment / all	4 / 8		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	6 / 734 (0.82%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

liver toxicity			
subjects affected / exposed	4 / 734 (0.54%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 734 (0.68%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Skin disorder			
subjects affected / exposed	1 / 734 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Wound healing problems			
subjects affected / exposed	4 / 734 (0.54%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrotoxicity			
subjects affected / exposed	4 / 734 (0.54%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
infection without neutropenia			
subjects affected / exposed	57 / 734 (7.77%)		
occurrences causally related to treatment / all	13 / 57		
deaths causally related to treatment / all	1 / 3		
infections with neutropenia			
subjects affected / exposed	9 / 734 (1.23%)		
occurrences causally related to treatment / all	5 / 9		
deaths causally related to treatment / all	1 / 2		
Product issues			
medical device complication			

subjects affected / exposed	2 / 734 (0.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	adverse events according to SAF		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 734 (4.50%)		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	33 / 734 (4.50%)		
occurrences (all)	33		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2007	After authorization of cetuximab (Erbitux®) as 5 mg/ml solution for infusion by the European Medicines Agency (EMA) (Doc.Ref. EMEA/CHMP/280402/2008) cetuximab was provided as 5 mg/ml solution for the trial instead of the previously used 2 mg/ml solution that had been used initially.
03 September 2008	• Trials had shown that patients with mutated KRAS did not respond to anti EGFR treatment. Treatment with cetuximab was to be confined to KRAS-wildtype patients. Thus the in- and exclusion criteria were amended accordingly to include only patients with KRAS wild-type. Patients with mutated KRAS had to discontinue treatment with cetuximab. • The planned primary statistical analysis was modified to take into account only patients with KRAS wild-type disease, whereas already included patients with mutated KRAS status would be analysed only by means of descriptive analyses. The sample size was increased from 147 to 284 evaluable patients per treatment arm. • Also, all subsequently as well as prior obtained tumour samples were to be analysed regarding the KRAS mutation status. • A variation for the cetuximab (Erbitux®) marketing authorization was authorized (Doc.Ref. EMEA/CHMP/280402/2008) in 2008. Additional indication of cetuximab: treatment of patients with epidermal growth factor receptor (EGFR) - expressing, KRAS wild-type metastatic colorectal cancer in combination with chemotherapy. Therefore cetuximab was no longer supplied as study medication, but had to be prescribed. • Additional collection of copies of CT images for planned independent review at a later time point.
25 January 2011	• Addition of a translational research project to search for predictors for response to cetuximab and bevacizumab in the treatment of mCRC patients. Pharmacogenetic factors were to be analysed in an additionally collected blood sample. • The accountability of the biostatistics and data management services were transferred from „Wissenschaftlicher Service Pharma (WiSP) GmbH“ to „ClinAssess GmbH“.
20 April 2012	• Two secondary endpoints were added: - Time to failure of strategy“ (TFS) for first-line treatment - Depth of remission (maximum percentage decrease of tumour size compared to baseline tumour size). Planned statistical analysis of the secondary endpoints was added. • From the updated SmPCs new information regarding safety was introduced for FOLFIRI, cetuximab and bevacizumab. • An independent radiological review for the evaluation of tumour response was established. Tumour response in the independent review was to be evaluated according to RECIST 1.1 (in contrast to local assessment of tumour response with RECIST 1.0) • K-RAS genotyping had revealed a proportion of 144 patients with mutated or unknown K-RAS genotype (patients included before Amendment 2) and actual data to the number of drop outs were evaluable. Thus, the number of patients was increased to 800 patients overall, to obtain the required 256 evaluable KRAS wild-type patients per treatment arm. • Duration of patient recruitment time was extended from 48 to 72 months.
19 April 2013	• Change from trial phase II to trial phase III according to the number of recruited patients

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/25088940