Clinical trial results:
Bi-weekly Cetuximab combined with FOLFOX-6 as first-line treatment in metastatic colorectal cancer patients with wild-type k-ras status

Summary

EudraCT number	2007-000460-24
Trial protocol	DE
Global end of trial date	23 September 2016

Results information

Result version number	v1 (current)
This version publication date	13 March 2020
First version publication date	13 March 2020
Summary attachment (see zip file)	SynpsosisCSR__2007-000460-24 (Cebifox_CSR_Synopsis_EudraCT 2007-000460-24.docx)

Trial information

Trial identification

Sponsor protocol code	TT1-2007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01051167
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Duisburg-Essen
Sponsor organisation address	Hufelandstraße 55, Essen, Germany, 45122
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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	20 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2016
Global end of trial reached?	Yes
Global end of trial date	23 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Response rate (using RECIST-Criteria vs 1.0)

Protection of trial subjects:

The treatment should be conducted exactly as described in the protocol. Any protocol deviation were reported. The recommendations of Good Clinical Practice (see ICH-GCP: International Conference on Harmonisation - Good Clinical Practice), valid since 17 January 1997, were met.

Background therapy:

Sedatives, antibiotics, analgesics, antihistamines, steroids, granulocyte-colony stimulating factor, erythropoetin, or other medications as well as red blood cells, platelets or fresh frozen plasma transfusions could be given to assist in the management of pain, infection, and other complications of the malignancy.
Patients had to be pre-medicated with an antihistamine and corticosteroid before receiving the first three infusions of cetuximab.
Premedication with an antihistamine and corticosteroid before subsequent infusions was recommended.
Patients could be pre-medicated before oxaliplatin infusions according to local standard routine

Evidence for comparator:

Since this was a single arm trial, no comparators were used.

Actual start date of recruitment	14 August 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	36
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Upon obtaining signed informed consent, screening evaluations were performed to confirm eligibility and to obtain baseline safety data.
Between 14-Aug-2009 (First patient in) and 21-Nov-2013 (Last patient in) 60 patients were registered by 6 sites (medical practices as well as hospitals) in Germany.

Pre-assignment

Screening details:

The selection of patients occurred through the investigator according to the inclusion and exclusion criteria after having informed the patient in writing and orally about the study and after the patient has signed the informed consent. These baseline examinations should be performed within 3 weeks before start of treatment.

Pre-assignment period milestones

Number of subjects started	57
Number of subjects completed	57

Period 1

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

Arms

Arm title	Cetuximab + Folfox-6

Arm description:

Biweekly Cetuximab in combination with a biweekly FOLFOX 6 regimen

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

After registration into the clinical trial patients received cetuximab 500 mg/m² as an intravenous infusion on day 1 every 2 weeks. Infusion time was 120 minutes for the first treatment and was reduced to 90 minutes for the second infusion and to 60 minutes for subsequent infusions.

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

Dosage and administration details:

85 mg oxaliplatin /m² body surface area was given as i.v. infusion for 2 hours every 2 weeks

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

Dosage and administration details:

400 mg folinic acid/m² was given as intravenous infusion over 120 minutes concurrently with oxaliplatin, d1, q14d

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

Dosage and administration details:

400 mg 5 - Fluoruracil /m² iv was given as bolus after Folinic Acid, d1, q14d
After bolus infusion, 2400 mg/m² 5-FU was applied as iv infusion over 46 h, d1, q14d

Number of subjects in period 1	Cetuximab + Folfox-6
Started	57
Completed	57

Baseline characteristics

Reporting groups

Reporting group title	Start of therapy

Reporting group description: -

Reporting group values	Start of therapy	Total	
Number of subjects	57	57	
Age categorical			
Male and female patients ≥ 18 years of age could be registered. There was no naximum age limit. Age of patients was calculated by subtracting year of birth from year of enrolment.			
Units: Subjects			
<30 years	2	2	
30-40 years	1	1	
41-50 years	8	8	
51-60 years	17	17	
61-70 years	17	17	
71-80 years	12	12	
Age continuous			
Units: years			
arithmetic mean	60		
standard deviation	± 1.67	-	
Gender categorical			
There was no preferred enrolment of men or women within this study. However, pregnant or breast-feeding women were excluded from participation.			
Units: Subjects			
Female	21	21	
Male	36	36	

Subject analysis sets

Subject analysis set title	ITT set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Received at least 1 administration of cetuximab

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

received at least 1 cycle of study medication

Subject analysis set title	PP set
Subject analysis set type	Per protocol

Subject analysis set description:

Received at least 5 cycles of study therapy

Reporting group values	ITT set	Safety set	PP set
Number of subjects	57	56	50
Age categorical			
Male and female patients ≥ 18 years of age could be registered. There was no naximum age limit. Age of patients was calculated by subtracting year of birth from year of enrolment.			
Units: Subjects			

<30 years	2	2	2
30-40 years	1	1	1
41-50 years	8	8	7
51-60 years	17	17	14
61-70 years	17	17	16
71-80 years	12	11	10
Age continuous			
Units: years			
arithmetic mean	60	59.7	59.8
standard deviation	± 1.67	± 1.67	± 1.8
Gender categorical			
There was no preferred enrolment of men or women within this study. However, pregnant or breast-feeding women were excluded from participation.			
Units: Subjects			
Female	21	21	19
Male	36	35	31

End points

End points reporting groups

Reporting group title	Cetuximab + Folfox-6
Reporting group description: Biweekly Cetuximab in combination with a biweekly FOLFOX 6 regimen	
Subject analysis set title	ITT set
Subject analysis set type	Intention-to-treat
Subject analysis set description: Received at least 1 administration of cetuximab	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: received at least 1 cycle of study medication	
Subject analysis set title	PP set
Subject analysis set type	Per protocol
Subject analysis set description: Received at least 5 cycles of study therapy	

Primary: Objective response rate (ORR) according to RECIST criteria

End point title	Objective response rate (ORR) according to RECIST criteria[1]
End point description: The primary target value of this study was the objective response rate, using RECIST criteria. Each set of tumor responses was assessed to determine the best overall response. ORR was defined by number of patients with CR+PR as best response.	
End point type	Primary
End point timeframe: Tumor assessment was perforemd at baseline and every 8 weeks during during study therapy; after last study treatment administration tumor asessment was performed every 3 months until end of follow-up.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Simon Two-Stage desgin. Altogether 37 patients of the ITT set had CR or PR as best response; this amounted to an ORR of 65%.
DCR (CR+PR+SD) was 84.1%. In the first stage 25 responders and in the second stage 35 responders were observed, which was more than the necessary number (≥13 responders in the first stage and ≥25 responders after completion of the second stage) to reject the null hypothesis H0: $p \leq 0.35$.

End point values	Cetuximab + Folfox-6	ITT set	Safety set	PP set
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	57	56	50
Units: number of patients				
Complete remission (CR)	1	1	1	1
Partial response (PR)	36	36	36	35
Stable disease (SD)	11	11	11	9
Progressive disease (PD)	5	5	5	3
Not evaluated	4	4	3	2
ORR (CR+PR)	37	37	37	36

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Patients with documented objective response, namely CR and PR, were included into this calculation.

End point type	Secondary

End point timeframe:

For this analysis patients were censored at time point of metastasectomy or loss to follow up.

End point values	Cetuximab + Folfox-6	ITT set	Safety set	PP set
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	37	37	36
Units: months				
median (confidence interval 95%)	10.28 (4.18 to 16.39)	10.28 (4.18 to 16.39)	10.28 (4.18 to 16.39)	10.28 (4.18 to 16.39)

Statistical analyses

No statistical analyses for this end point

Secondary: Metastasectomy rate

End point title	Metastasectomy rate

End point description:

Proportions of patients who were able to undergo complete metastasectomy after study treatment

End point type	Secondary

End point timeframe:

From start of therapy until end of study treatment

End point values	Cetuximab + Folfox-6	ITT set	Safety set	PP set
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	57	56	50
Units: number of patients	19	19	19	18

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Progression free survival of a patient was defined as the time in months from registration until PD is observed or death occurs due to any cause within 90 days after the last tumor assessment or registration. Patients not known to progress or die were censored at their date of last contact or 90 days after the last tumor assessment or registration, whichever came first.

End point type	Secondary

End point timeframe:

From registration until observed PD or death due to any cause within 90 days after the last tumor assessment or registration

End point values	Cetuximab + Folfox-6	ITT set	Safety set	PP set
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	57	56	50
Units: months				
median (confidence interval 95%)	10.05 (8.33 to 11.775)	10.05 (8.33 to 11.775)	10.81 (9.10 to 12.52)	10.94 (9.39 to 12.49)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

OS (in months) was easured from the date of registration until death occurs due to any cause. OS for subjects not known to die will be censored at their date of last contact.

End point type	Secondary

End point timeframe:

From the date of registration until death occurs due to any cause.

End point values	Cetuximab + Folfox-6	ITT set	Safety set	PP set
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	57	56	50
Units: months				
median (confidence interval 95%)	28.65 (18.86 to 38.44)	28.65 (18.86 to 38.44)	29.37 (17.03 to 41.71)	29.37 (17.33 to 41.41)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of signing informed consent until end of treatment

Adverse event reporting additional description:

Toxicities were defined according to the NCI-CTC-Toxicity Criteria version 3.0. Any AE that occured in the course of a clinical study were monitored and followed up until
the End of Study Visit.
Only AEs of special interest were taken into account.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	ITT set

Reporting group description: -

Serious adverse events	ITT set		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 57 (33.33%)		
number of deaths (all causes)	36		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Asthenia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	4 / 57 (7.02%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Stricture/stenosis GI - Colon sigmoideum				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Nausea			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rosacea			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Urinary tract obstruction			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyelonephritis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device malfunction			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	ITT set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 57 (100.00%)		
Investigations			
Lipase			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	12		
Amylase			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Hypocalcaemia			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	6		
Nervous system disorders			
Peripheral sensory neuropathy/Nervous system disorder			
subjects affected / exposed	31 / 57 (54.39%)		
occurrences (all)	51		
Peripheral motor neuropathy			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	5		
Platelet count decreased			
subjects affected / exposed	14 / 57 (24.56%)		
occurrences (all)	34		
White blood cell count decreased			
subjects affected / exposed	17 / 57 (29.82%)		
occurrences (all)	22		
Granulocytes count decreased			
subjects affected / exposed	18 / 57 (31.58%)		
occurrences (all)	31		
Haemoglobin (Anemia)			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	14		
General disorders and administration site conditions			
Adverse drug reaction/Hypersensitivity			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	7		
Chills/Pyrexia			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	9		

Cytokine release syndrome subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Eyelid disorder subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Lacrimation increased subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Uveitis subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 5		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	9 / 57 (15.79%) 9		
Diarrhoea subjects affected / exposed occurrences (all)	24 / 57 (42.11%) 32		
Nausea/Malaise subjects affected / exposed occurrences (all)	28 / 57 (49.12%) 56		
Vomiting subjects affected / exposed occurrences (all)	8 / 57 (14.04%) 11		
Stomatitis/Oesophagitis subjects affected / exposed occurrences (all)	15 / 57 (26.32%) 19		
Hepatobiliary disorders			

Transaminases abnormal subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 7		
Blood alkaline phosphatase subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform subjects affected / exposed occurrences (all)	35 / 57 (61.40%) 53		
Dry skin subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 3		
Eczema subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
rash (Exfoliative, maculo-papular) /Folliculitis subjects affected / exposed occurrences (all)	23 / 57 (40.35%) 32		
Skin disorder/ haemorrhage/ hyperpigmentation subjects affected / exposed occurrences (all)	9 / 57 (15.79%) 14		
Skin fissures subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 3		
Nail bed inflammation/nail disorder subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4		
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	10 / 57 (17.54%) 15		
Pruritus subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Infections and infestations			

Febrile infection			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	3		
Infection			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Neutropenic infection			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Appetite lost			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Cachexia			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	9		
Weight decreased			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2009	Change in time points of blood sampling for translational project Change in patient's questionnaires
10 February 2010	Prolongation of recruiting period Change in time points of blood sampling for translational research project (at baseline and at administration of second study treatment cycle No central K-RAS assessment
09 June 2010	Chamge of exclusion criteria
27 December 2011	Change of sponsor representative and coordinationg investigator

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported