Clinical trial results:
Intra-hepatic chemotherapy with oxaliplatin every second week in combination with systemic gemcitabine and capecitabine in combination with cetuximab in patient with non-resectable liver metastases from cholangiocarcinoma. A phase II trial.

Summary

EudraCT number	2010-020188-19
Trial protocol	DK
Global end of trial date	18 February 2016

Results information

Result version number	v1 (current)
This version publication date	04 January 2020
First version publication date	04 January 2020
Summary attachment (see zip file)	2010-020188-19 (article.pdf)

Trial information

Trial identification

Sponsor protocol code	GI 1003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01247337
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herlev Hospital
Sponsor organisation address	Herlev Ringvej 75, Herlev, Denmark, 2730
Public contact	Dorte Nielsen, Department of Oncology, Herlev Hospital, +45 38682344, Dorte.nielsen.01@regionh.dk
Scientific contact	Dorte Nielsen, Department of Oncology, Herlev Hospital, +45 38682344, Dorte.nielsen.01@regionh.dk

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	18 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 February 2016
Global end of trial reached?	Yes
Global end of trial date	18 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary endpoint

Progression free survival

Protection of trial subjects:

Eligibility criteria, regular/standard safety monitoring during treatment

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2011
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	Denmark: 56
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	26
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was open from Februar 2011 to August 2013, Patients were included at single site (Herlev Hospital) in Denmark

Pre-assignment

Screening details:

Patients with non-resectable or recurrent biliary tract carcinoma, ECOG performance 0-1, without previous chemotherapy in palliative setting.

Period 1

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

Blinding implementation details:

NA

Arms

Are arms mutually exclusive?	Yes
Arm title	TACE

Arm description:

Chemotherapy consisting of continuous capecitabine in combination with oxaliplatin, gemcitabine and cetuximab every 2 weeks.
For this group of patients oxaliplatin was given intrahepatic (using TACE) every 4 weeks/every 2nd cycle (max 6 applications), the remaining oxaliplatin administration were systemic (iv)

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

Dosage and administration details:

50 mg/m2 every 2 weeks, alternately intrahepatic and intravenous for the first 12 cycles (max 6 intrahepatic applications)

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

650 mg/m2 BID continously

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

Dosage and administration details:

1000 mg/m2 q2w

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

Dosage and administration details:

500 mg/m2 q2w

Arm title	Systemic

Arm description:

Chemotherapy consisting of continuous capecitabine in combination with oxaliplatin, gemcitabine and cetuximab every 2 weeks. Oxaliplatin given iv in all cycles

Arm type	Experimental
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:

50 mg/m2 every 2 weeks

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

Dosage and administration details:

1000 mg/m2 q2w

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

650 mg/m2 BID continously

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

Dosage and administration details:

500 mg/m2 q2w

Number of subjects in period 1	TACE	Systemic
Started	3	53
Completed	2	42
Not completed	1	11
Adverse event, serious fatal	-	3
Consent withdrawn by subject	-	1

Adverse event, non-fatal	1	4
Protocol deviation	-	3

Baseline characteristics

Reporting groups	
Reporting group title	TACE
Reporting group description:	
Chemotherapy consisting of continuous capecitabine in combination with oxaliplatin, gemcitabine and cetuximab every 2 weeks. For this group of patients oxaliplatin was given intrahepatic (using TACE) every 4 weeks/every 2nd cycle (max 6 applications), the remaining oxaliplatin administration were systemic (iv)	
Reporting group title	Systemic
Reporting group description:	
Chemotherapy consisting of continuous capecitabine in combination with oxaliplatin, gemcitabine and cetuximab every 2 weeks. Oxaliplatin given iv in all cycles	

Reporting group values	TACE	Systemic	Total
Number of subjects	3	53	56
Age categorical Units: Subjects			
Adults (18-64 years)	2	24	26
From 65-84 years	1	29	30
Gender categorical Units: Subjects			
Female	2	32	34
Male	1	21	22

End points

End points reporting groups

Reporting group title	TACE

Reporting group description:

Chemotherapy consisting of continuous capecitabine in combination with oxaliplatin, gemcitabine and cetuximab every 2 weeks.
For this group of patients oxaliplatin was given intrahepatic (using TACE) every 4 weeks/every 2nd cycle (max 6 applications), the remaining oxaliplatin administration were systemic (iv)

Reporting group title	Systemic

Reporting group description:

Chemotherapy consisting of continuous capecitabine in combination with oxaliplatin, gemcitabine and cetuximab every 2 weeks. Oxaliplatin given iv in all cycles

Primary: PFS

End point title	PFS[1][2]

End point description:

End point type	Primary

End point timeframe:

treatment start to date of progression or death

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: exploratory phase 2 trial

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 3 patients included that received TACE, therefore median PFS not analysed

End point values	Systemic			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: months				
median (confidence interval 95%)	8.5 (7.3 to 9.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: OS

End point title	OS[3]

End point description:

End point type	Secondary

End point timeframe:

treatment start to date of death (patients alive censored Jun2015)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 3 patients included that received TACE, therefore median OS not analysed

End point values	Systemic			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: months				
median (confidence interval 95%)	12.8 (8.8 to 16.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate

End point title	Response rate

End point description:

End point type	Secondary

End point timeframe:

Disease assessment every 8 weeks

End point values	TACE	Systemic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	53		
Units: number of patients				
CR	0	1		
PR	1	11		
SD	2	31		
PD	0	6		
Not evaluable	0	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment start to 28 days after last treatment

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	3

Reporting groups

Reporting group title	TACE

Reporting group description:

Chemotherapy consisting of continuous capecitabine in combination with oxaliplatin, gemcitabine and cetuximab every 2 weeks.
For this group of patients oxaliplatin was given intrahepatic (using TACE) every 4 weeks/every 2nd cycle (max 6 applications), the remaining oxaliplatin administration were systemic (iv)

Reporting group title	Systemic

Reporting group description:

Chemotherapy consisting of continuous capecitabine in combination with oxaliplatin, gemcitabine and cetuximab every 2 weeks. Oxaliplatin given iv in all cycles

Serious adverse events	TACE	Systemic	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	24 / 53 (45.28%)	
number of deaths (all causes)	3	50	
number of deaths resulting from adverse events	0	3	
Injury, poisoning and procedural complications			
Thoracic haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture - zygomatic bone			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	7 / 53 (13.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 3 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death not associated with CTCAE term			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain, stomach			

subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
allergic reaction			
subjects affected / exposed	0 / 3 (0.00%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer	Additional description: associated with bleeding		
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal varices hemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cholangitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 3 (0.00%)	6 / 53 (11.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Enteritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TACE	Systemic	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	53 / 53 (100.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	7 / 53 (13.21%)	
occurrences (all)	0	7	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	9 / 53 (16.98%)	
occurrences (all)	0	9	
Amylase increased			
subjects affected / exposed	0 / 3 (0.00%)	9 / 53 (16.98%)	
occurrences (all)	0	9	
Alkaline Phosphastase increased			
subjects affected / exposed	0 / 3 (0.00%)	6 / 53 (11.32%)	
occurrences (all)	0	6	
Neutrophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)	4 / 53 (7.55%)	
occurrences (all)	1	4	
Platelet count decreased			

subjects affected / exposed	1 / 3 (33.33%)	9 / 53 (16.98%)	
occurrences (all)	1	9	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 3 (100.00%)	40 / 53 (75.47%)	
occurrences (all)	3	40	
Dysaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	7 / 53 (13.21%)	
occurrences (all)	0	7	
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	36 / 53 (67.92%)	
occurrences (all)	1	36	
Fever			
subjects affected / exposed	1 / 3 (33.33%)	10 / 53 (18.87%)	
occurrences (all)	1	10	
Pain			
subjects affected / exposed	0 / 3 (0.00%)	18 / 53 (33.96%)	
occurrences (all)	0	18	
flu like symptoms			
subjects affected / exposed	0 / 3 (0.00%)	5 / 53 (9.43%)	
occurrences (all)	0	5	
Weight loss			
subjects affected / exposed	0 / 3 (0.00%)	7 / 53 (13.21%)	
occurrences (all)	0	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	13 / 53 (24.53%)	
occurrences (all)	0	13	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 3 (0.00%)	15 / 53 (28.30%)	
occurrences (all)	0	15	

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	41 / 53 (77.36%)	
occurrences (all)	1	41	
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	20 / 53 (37.74%)	
occurrences (all)	1	20	
Diarrhoea			
subjects affected / exposed	3 / 3 (100.00%)	20 / 53 (37.74%)	
occurrences (all)	3	20	
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	25 / 53 (47.17%)	
occurrences (all)	0	25	
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	4 / 53 (7.55%)	
occurrences (all)	0	4	
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	7 / 53 (13.21%)	
occurrences (all)	0	7	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 3 (66.67%)	36 / 53 (67.92%)	
occurrences (all)	2	36	
Nail changes			
subjects affected / exposed	1 / 3 (33.33%)	26 / 53 (49.06%)	
occurrences (all)	1	26	
Acne			
subjects affected / exposed	3 / 3 (100.00%)	38 / 53 (71.70%)	
occurrences (all)	3	38	
Dry skin			
subjects affected / exposed	1 / 3 (33.33%)	16 / 53 (30.19%)	
occurrences (all)	1	16	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 3 (0.00%)	5 / 53 (9.43%)	
occurrences (all)	0	5	

Metabolism and nutrition disorders anorexia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	 2 / 3 (66.67%) 2 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	 9 / 53 (16.98%) 9 4 / 53 (7.55%) 4 4 / 53 (7.55%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2011	- protocol expanded to include systemic treatment with oxaliplatin in combination with capecitabine, gemcitabine and cetuximab to patients with extrahepatic disease (50 patients) - Dosis of oxaliplatin with 50 mg/m2 implemented This amendment of the initial protocol was implemented before recruitment was started.
18 October 2011	- possibility to use a permanent catheter for intrahepatic treatment was discontinued (for safety reason based on clinical experience outside the trial - no patient had received intrahepatic treatment via permanent catheter) - with this amendment 100 patients for systemic and 50 patient for intrahepatic treatment were planned.
12 January 2012	- maximum of 6 intrahepatic administrations of oxaliplatin

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only 3 patients could be included to receive intrahepatic treatment with oxaliplatin, 53 patients were included to receive systemic oxaliplatin in combination with capecitabine, gemcitabine and cetuximab.

Notes: