



## Clinical trial results:

### Randomized 1. Line treatment with gemcitabine, capecitabine, oxaliplatin vs gemcitabin and cisplatin to patients with cholangiocarcinoma.

#### Summary

EudraCT number	2013-004854-46
Trial protocol	DK
Global end of trial date	01 May 2019

#### Results information

Result version number	v1 (current)
This version publication date	17 September 2020
First version publication date	17 September 2020

#### Trial information

##### Trial identification

Sponsor protocol code	GI 1333
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##### Additional study identifiers

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

Notes:

##### Sponsors

Sponsor organisation name	Herlev University Hospital, Department of Oncology
Sponsor organisation address	Herlev Ringvej 75, Herlev, Denmark, 2730
Public contact	Oncology Department, Herlev University Hospital, 0045 38682329, ole.larsen@regionh.dk
Scientific contact	Oncology Department, Herlev University Hospital, 0045 38682329, ole.larsen@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	30 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2019
Global end of trial reached?	Yes
Global end of trial date	01 May 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Progression free survival

Protection of trial subjects:

Patients that signed informed consent and fulfilling eligibility criteria were included. Continued monitoring of standard safety parameters during treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 June 2014
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: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	47
From 65 to 84 years	52
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

The trial was opened for recruitment in June 2014 and closed for enrollment in November 2017 per protocol. Patients were included at 2 sites in Denmark.

### Pre-assignment

Screening details:

Eligible patients were 18 years or older with histopathological diagnosis of nonresectable, recurrent, or metastatic BTC or a cytologic diagnosis in combination with radiological findings. Intrahepatic, perihilar, extrahepatic, and gallbladder cancers could be included—but not ampullary cancer. ECOG PS 0 or 1, bilirubin not above 2xULN.

### Pre-assignment period milestones

Number of subjects started	100
Intermediate milestone: Number of subjects	pre-treatment: 100
Number of subjects completed	96

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 2
Reason: Number of subjects	rapid progression of disease: 2

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	CapOxGem

Arm description:

Oxaliplatin and gemcitabine every 2 weeks combined with continuous capecitabine

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:

oxaliplatin 50 mg/m<sup>2</sup> every second week (infusion time of 30 min) until progression of disease

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:

gemcitabine 1000 mg/m<sup>2</sup> every second week (infusion time of 30 min) until progression of disease

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: capecitabine 650 mg/m <sup>2</sup> twice-daily, continuously until progression of disease	
<b>Arm title</b>	CisGem

Arm description:

Cisplatin and Gemcitabine on day 1 and 8 of each 3-week cycle, until progression of disease

Arm type	Active comparator
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

cisplatin 25 mg/m<sup>2</sup> (infusion time of 60 min) on day 1 and day 8, repeated every 3 weeks until progression of disease (with restriction to accumulated dose of max 400 mg/m<sup>2</sup>)

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:

gemcitabine 1000 mg/m<sup>2</sup> (infusion time of 30 min) on day 1 and day 8, repeated every 3 weeks until progression of disease

<b>Number of subjects in period 1</b> <sup>[1]</sup>	CapOxGem	CisGem
Started	47	49
Completed	41	38
Not completed	6	11
Adverse event, serious fatal	-	1
Physician decision	-	1
Adverse event, non-fatal	4	7
early death	2	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 4 patient did not complete pre-treatment period

## Baseline characteristics

### Reporting groups

Reporting group title	CapOxGem
Reporting group description: Oxaliplatin and gemcitabine every 2 weeks combined with continuous capecitabine	
Reporting group title	CisGem
Reporting group description: Cisplatin and Gemcitabine on day 1 and 8 of each 3-week cycle, until progression of disease	

Reporting group values	CapOxGem	CisGem	Total
Number of subjects	47	49	96
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	65	65	
full range (min-max)	21 to 85	39 to 82	-
Gender categorical			
Units: Subjects			
Female	24	26	50
Male	23	23	46
ECOG performance status			
Units: Subjects			
ECOG PS 0	23	23	46
ECOG PS 1	24	26	50

## End points

### End points reporting groups

Reporting group title	CapOxGem
Reporting group description:	Oxaliplatin and gemcitabine every 2 weeks combined with continuous capecitabine
Reporting group title	CisGem
Reporting group description:	Cisplatin and Gemcitabine on day 1 and 8 of each 3-week cycle, until progression of disease

### Primary: Progression free Survival

End point title	Progression free Survival <sup>[1]</sup>
End point description:	

End point type	Primary
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End point timeframe:

Scans were performed every 12 weeks until progression of disease

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: Sample size too small to compare the groups.

End point values	CapOxGem	CisGem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: months				
median (confidence interval 95%)	5.7 (3.0 to 7.8)	7.3 (6.0 to 8.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

End point title	Overall Survival
End point description:	

End point type	Secondary
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End point timeframe:

time from randomisation to death (censoring at database lock Aug 2019)

<b>End point values</b>	CapOxGem	CisGem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: months				
median (confidence interval 95%)	8.7 (6.5 to 11.2)	12.0 (8.3 to 16.7)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Tumor response

End point title	Tumor response
End point description:	
End point type	Secondary
End point timeframe:	
Tumor assessments were performed every 12 weeks during treatment	

<b>End point values</b>	CapOxGem	CisGem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: subjects				
Complete Response	0	0		
Partial Response	8	8		
Stable Disease	20	31		
Progression	14	5		
Not assessable	5	5		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From date of first treatment to 28 days after last treatment with the trial

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI-CTCAE
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Dictionary version	4
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### Reporting groups

Reporting group title	CapOxGem
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Reporting group description:

Oxaliplatin and gemcitabine every 2 weeks combined with continuous capecitabine

Reporting group title	CisGem
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Reporting group description:

Cisplatin and Gemcitabine on day 1 and 8 of each 3-week cycle, until progression of disease

<b>Serious adverse events</b>	CapOxGem	CisGem	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 47 (34.04%)	19 / 49 (38.78%)	
number of deaths (all causes)	44	46	
number of deaths resulting from adverse events	0	2	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 47 (4.26%)	6 / 49 (12.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 49 (2.04%)	
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 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 47 (4.26%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction	Additional description: patient in CapOxGem - allergic reaction to oxaliplatin patient in CisGem- allergic reaction to concomitant medication (not study treatment)		
subjects affected / exposed	1 / 47 (2.13%)	12 / 49 (24.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 47 (0.00%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: as symptom for COPD exacerbation		
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-reactive protein increased			

subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Injury, poisoning and procedural complications</b>			
Fall			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cardiac disorders</b>			
Cardiotoxicity			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
	Additional description: Non-STEMI		
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nervous system disorders</b>			
Seizure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

stroke			
subjects affected / exposed	1 / 47 (2.13%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oral hemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 47 (6.38%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 47 (4.26%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatorenal syndrome			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
ureteral stones			

subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
<b>Infection</b>	Additional description: Summarised term Infection, includes cases of biliary tract infection, gastroenteritis, infection with unknow focus, pancreatitis, urinary tract infection		
subjects affected / exposed	3 / 47 (6.38%)	5 / 49 (10.20%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Sepsis</b>			
subjects affected / exposed	3 / 47 (6.38%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bacteraemia</b>			
subjects affected / exposed	2 / 47 (4.26%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pneumonia</b>			
subjects affected / exposed	0 / 47 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Abscess</b>			
subjects affected / exposed	0 / 47 (0.00%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
<b>hyperglycemia</b>			
subjects affected / exposed	2 / 47 (4.26%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hypercalcaemia</b>			
subjects affected / exposed	1 / 47 (2.13%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	CapOxGem	CisGem	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 47 (100.00%)	49 / 49 (100.00%)	
Investigations			
Neutropenia			
subjects affected / exposed	4 / 47 (8.51%)	30 / 49 (61.22%)	
occurrences (all)	4	30	
Thrombocytopenia			
subjects affected / exposed	10 / 47 (21.28%)	16 / 49 (32.65%)	
occurrences (all)	10	16	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	7 / 47 (14.89%)	12 / 49 (24.49%)	
occurrences (all)	7	12	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	41 / 47 (87.23%)	24 / 49 (48.98%)	
occurrences (all)	41	24	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 47 (21.28%)	17 / 49 (34.69%)	
occurrences (all)	10	17	
Febrile neutropenia			
subjects affected / exposed	0 / 47 (0.00%)	5 / 49 (10.20%)	
occurrences (all)	0	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	37 / 47 (78.72%)	36 / 49 (73.47%)	
occurrences (all)	37	36	
Ear and labyrinth disorders			

Tinnitus subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	10 / 49 (20.41%) 10	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	35 / 47 (74.47%) 35	34 / 49 (69.39%) 34	
Vomiting subjects affected / exposed occurrences (all)	20 / 47 (42.55%) 20	15 / 49 (30.61%) 15	
Diarrhoea subjects affected / exposed occurrences (all)	19 / 47 (40.43%) 19	9 / 49 (18.37%) 9	
Hepatobiliary disorders Biliary tract disorder subjects affected / exposed occurrences (all)	9 / 47 (19.15%) 9	2 / 49 (4.08%) 2	
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	20 / 47 (42.55%) 20	0 / 49 (0.00%) 0	
Infections and infestations Infection subjects affected / exposed occurrences (all)	33 / 47 (70.21%) 33	40 / 49 (81.63%) 40	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2015	In treatment arm CisGem, the treatment with Cisplatin was limited to an accumulated dose of max 400 mg/m <sup>2</sup>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32698410>