



Clinical trial results:

Intra-hepatic and systemic chemotherapy with or without antibody for patients with non-resectable liver metastasis from solid tumours

Summary

EudraCT number	2011-000273-31
Trial protocol	DK
Global end of trial date	31 May 2018

Results information

Result version number	v1 (current)
This version publication date	16 September 2020
First version publication date	16 September 2020

Trial information

Trial identification

Sponsor protocol code	AA1023
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01511146
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herlev University Hospital
Sponsor organisation address	Herlev Ringvej 75, Herlev, Denmark, 2730
Public contact	Dorte Nielsen, Department of Oncology, +45 38682344, Dorte.nielsen.01@regionh.dk
Scientific contact	Dorte Nielsen, Department of Oncology, +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	31 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2018
Global end of trial reached?	Yes
Global end of trial date	31 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Tumour response (RECIST version 1.1)

Protection of trial subjects:

Patients with informed consent and fulfilling eligibility criteria were included. Continues monitoring of standard safety parameters during treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 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: 70
Worldwide total number of subjects	70
EEA total number of subjects	70

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)	41
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients recruited at single site at Herlev Hospital, Department of Oncology, Denmark, Recruitment was open from June 2011 to November 2016

Pre-assignment

Screening details:

Patients with histologically confirmed solid tumor with metastases in liver were allowed. Patients were included if the liver metastases were not eligible for local ablation by RFA, SBRT, or surgery evaluated at a MDT conference and had <70% of the liver affected.

Pre-assignment period milestones

Number of subjects started	70
Number of subjects completed	65

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 3
Reason: Number of subjects	Intrahepatic administration not possible: 2

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FOLFOX

Arm description:

For patients with colorectal cancer without prior treatment with oxaliplatin:
Regimen FOLFOX with alternating systemic and intrahepatic application of oxaliplatin (max 6 intrahepatic applications)
Patients with KRAS wildtype tumor additionally received cetuximab

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:

85 mg/m² every second week,
application no. 1,3,5,7,9,11 intravenous
application no 2,4,6,8,10,12 intrahepatic

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

Dosage and administration details: 400 mg/m ² bolus and 2400 mg/m ² over 46 hours, every second week	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m ² every second week	
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 500 mg/m ² every 2 weeks	
Arm title	CaMiGem
Arm description: For patients with other solid tumors or patients with colorectal cancer, that had received oxaliplatin before Regimen consisting of Capecitabine + intrahepatic application of gemcitabine and mitomycin	
Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details: first three patients recieved capecitabine 500 mg/m ² twice a day continuously, other patients received capecitabine 650 mg/m ² twice a day continuously	
Investigational medicinal product name	Mitomycin C
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intrahepatic use
Dosage and administration details: First three + three patients to receive 5 mg/m ² every 4 weeks, other patients to receive 6 mg/m ² every 4 weeks	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intrahepatic use
Dosage and administration details: All patients to receive 800 mg/m ² every 4 weeks	

Number of subjects in period 1^[1]	FOLFOX	CaMiGem
Started	45	20
Completed	36	17
Not completed	9	3
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Physician decision	2	2
Adverse event, non-fatal	5	1

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: worldwide enrolled number includes 5 patients that signed consent and registered for the trial, but did not complete pre-assignment period

Baseline characteristics

Reporting groups

Reporting group title	FOLFOX
Reporting group description:	
For patients with colorectal cancer without prior treatment with oxaliplatin: Regimen FOLFOX with alternating systemic and intrahepatic application of oxaliplatin (max 6 intrahepatic applications) Patients with KRAS wildtype tumor additionally received cetuximab	
Reporting group title	CaMiGem
Reporting group description:	
For patients with other solid tumors or patients with colorectal cancer, that had received oxaliplatin before Regimen consisting of Capecitabine + intrahepatic application of gemcitabine and mitomycin	

Reporting group values	FOLFOX	CaMiGem	Total
Number of subjects	45	20	65
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	60	62	
full range (min-max)	49 to 82	39 to 80	-
Gender categorical Units: Subjects			
Female	18	6	24
Male	27	14	41
Primary cancer Units: Subjects			
Colorectal Cancer	45	15	60
Ovarian Cancer	0	1	1
Pancreatic Cancer	0	1	1
Cholangiocarcinoma	0	1	1
Duodenal Cancer	0	1	1
Sarcoma	0	1	1
KRAS mutation status Units: Subjects			
Wildtype	23	10	33
Mutated	22	4	26
Unknown/not relevant	0	6	6

ECOG performance status			
Units: Subjects			
ECOG 0	39	16	55
ECOG 1	6	4	10

End points

End points reporting groups

Reporting group title	FOLFOX
Reporting group description: For patients with colorectal cancer without prior treatment with oxaliplatin: Regimen FOLFOX with alternating systemic and intrahepatic application of oxaliplatin (max 6 intrahepatic applications) Patients with KRAS wildtype tumor additionally received cetuximab	
Reporting group title	CaMiGem
Reporting group description: For patients with other solid tumors or patients with colorectal cancer, that had received oxaliplatin before Regimen consisting of Capecitabine + intrahepatic application of gemcitabine and mitomycin	

Primary: Tumor response

End point title	Tumor response ^[1]
End point description: Tumor response evaluation according to RECIST v1.1	
End point type	Primary
End point timeframe: Tumor evaluation was performed at baseline and every 8 weeks during treatment and every 3 months in FU	

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: This was a phase 2 study with 2 arm investigating 2 different drug combinations. It was not planned to compare these combination.

End point values	FOLFOX	CaMiGem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	20		
Units: Subjects				
CR	1	0		
PR	36	1		
SD	6	9		
PD	1	10		
Not evaluable	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free Survival

End point title	Progression free Survival
End point description: PFS is defined as the period from the first treatment to the first observation of disease progression or death of any cause, whichever came first, or censored at last follow-up. Median and CI determined using Kaplan-Meier.	

End point type	Secondary
End point timeframe:	
Tumor evaluation was performed every 8 weeks during treatment and every 3 months in FU,	

End point values	FOLFOX	CaMiGem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	20		
Units: months				
median (confidence interval 95%)	12.9 (10.2 to 15.6)	3.1 (1.8 to 4.4)		

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:

OS was calculated as the time from the first treatment to death from any cause or censored at last follow-up.

End point values	FOLFOX	CaMiGem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	20		
Units: months				
median (confidence interval 95%)	38.7 (33.0 to 44.3)	8.5 (6.7 to 10.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: No. of patients receiving liver resection/RFA

End point title	No. of patients receiving liver resection/RFA
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End point description:

End point type	Secondary
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End point timeframe:

Resectability was assessed at time of tumor evaluation during treatment.

End point values	FOLFOX	CaMiGem		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	20		
Units: subjects				
Liver resection/RFA performed	26	0		
no resection	19	20		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start of treatment until 30 days after last treatment

Adverse event reporting additional description:

Apart from Serious adverse events, only adverse events assessed as treatment-related are listed.

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	FOLFOX
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Reporting group description:

For patients with colorectal cancer without prior treatment with oxaliplatin:

Regimen FOLFOX with alternating systemic and intrahepatic application of oxaliplatin (max 6 intrahepatic applications)

Patients with KRAS wildtype tumor additionally received cetuximab

Reporting group title	CaMiGem
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Reporting group description:

For patients with other solid tumors or patients with colorectal cancer, that had received oxaliplatin before

Regimen consisting of Capecitabine + intrahepatic application of gemcitabine and mitomycin

Serious adverse events	FOLFOX	CaMiGem	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 50 (44.00%)	5 / 20 (25.00%)	
number of deaths (all causes)	33	20	
number of deaths resulting from adverse events	1	0	
Investigations			
elevated liver enzymes			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Petidin toxication			
subjects affected / exposed	0 / 50 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
displaced rectal stent			

subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
drop foot			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amputation lower leg			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain related to TACE treatment			
subjects affected / exposed ^[1]	1 / 45 (2.22%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 50 (8.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
vein occlusion eye			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac disorder			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 50 (4.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-ST-elevation myocardial infarction			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (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			
Infarction cerebral			
subjects affected / exposed	0 / 50 (0.00%)	1 / 20 (5.00%)	
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			
Fever			
subjects affected / exposed	2 / 50 (4.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction to cetuximab			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Subileus			

subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess cholecystit			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 50 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer			
subjects affected / exposed	2 / 50 (4.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 20 (5.00%)	
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			
Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 50 (4.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			

subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (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			
Sepsis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 50 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Only 45 patient recieved TACE, the additional 5 patient did no complete pre-assignment period

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

Non-serious adverse events	FOLFOX	CaMiGem	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 50 (90.00%)	20 / 20 (100.00%)	
Investigations			
Thrombocytopenia			

subjects affected / exposed ^[2] occurrences (all)	14 / 45 (31.11%) 14	2 / 20 (10.00%) 2	
Neutropenia subjects affected / exposed ^[3] occurrences (all)	23 / 45 (51.11%) 23	1 / 20 (5.00%) 1	
Aspartate aminotransferase increased subjects affected / exposed ^[4] occurrences (all)	13 / 45 (28.89%) 13	0 / 20 (0.00%) 0	
Alanine aminotransferase increased subjects affected / exposed ^[5] occurrences (all)	10 / 45 (22.22%) 10	0 / 20 (0.00%) 0	
Alkaline phosphatase increased subjects affected / exposed ^[6] occurrences (all)	10 / 45 (22.22%) 10	1 / 20 (5.00%) 1	
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed ^[7] occurrences (all)	41 / 45 (91.11%) 41	6 / 20 (30.00%) 6	
General disorders and administration site conditions Fatigue subjects affected / exposed ^[8] occurrences (all)	31 / 45 (68.89%) 31	5 / 20 (25.00%) 5	
Fever subjects affected / exposed ^[9] occurrences (all)	8 / 45 (17.78%) 8	1 / 20 (5.00%) 1	
Flu-like symptoms subjects affected / exposed ^[10] occurrences (all)	9 / 45 (20.00%) 9	1 / 20 (5.00%) 1	
Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed ^[11] occurrences (all)	0 / 45 (0.00%) 0	1 / 20 (5.00%) 1	
Anaemia subjects affected / exposed ^[12] occurrences (all)	8 / 45 (17.78%) 8	2 / 20 (10.00%) 2	
Immune system disorders			

Allergic reaction	Additional description: Allergic reactions were seen to cetuximab 2 cases and oxaliplatin 3 cases		
	subjects affected / exposed ^[13]	5 / 45 (11.11%)	0 / 20 (0.00%)
	occurrences (all)	5	0
Gastrointestinal disorders			
Nausea			
	subjects affected / exposed ^[14]	32 / 45 (71.11%)	3 / 20 (15.00%)
	occurrences (all)	32	3
Vomiting			
	subjects affected / exposed ^[15]	16 / 45 (35.56%)	0 / 20 (0.00%)
	occurrences (all)	16	0
Diarrhoea			
	subjects affected / exposed ^[16]	18 / 45 (40.00%)	5 / 20 (25.00%)
	occurrences (all)	18	5
Stomatitis			
	subjects affected / exposed ^[17]	28 / 45 (62.22%)	5 / 20 (25.00%)
	occurrences (all)	28	5
Anorexia			
	subjects affected / exposed ^[18]	5 / 45 (11.11%)	1 / 20 (5.00%)
	occurrences (all)	5	1
Hepatobiliary disorders			
Pain in liver after TACE			
	subjects affected / exposed ^[19]	26 / 45 (57.78%)	6 / 20 (30.00%)
	occurrences (all)	26	6
Liver abscess			
	subjects affected / exposed ^[20]	0 / 45 (0.00%)	1 / 20 (5.00%)
	occurrences (all)	0	1
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
	subjects affected / exposed	26 / 50 (52.00%)	8 / 20 (40.00%)
	occurrences (all)	26	8
Acne			
	Additional description: Only 23 patients in FOLFOX arm received additionally cetuximab, which the AE is related to.		
	subjects affected / exposed ^[21]	23 / 45 (51.11%)	0 / 20 (0.00%)
	occurrences (all)	23	0
Infections and infestations			
Infection without neutropenia			

subjects affected / exposed ^[22]	4 / 45 (8.89%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed ^[23]	1 / 45 (2.22%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Hypomagnesaemia			
subjects affected / exposed ^[24]	6 / 45 (13.33%)	1 / 20 (5.00%)	
occurrences (all)	6	1	

Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Total number exposed includes the patient that did not complete pre-assignment period as

those are included in reporting of Serious Events, however non-serious event are reported for patient in the treatment period only.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2011	- Option to use permanent intrahepatic cateter omitted - Patients to receive diary to record pain
12 January 2012	Clarification that maximum of 6 intrahepatic applications of chemotherapy will be given
16 February 2016	Prolongation of recruitment and study timelines

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/30999314>