

**Clinical trial results:****Assessment of histopathological response to combination chemotherapy with Oxaliplatin, Irinotecan, Fluorouracil and Bevacizumab in patients with peritoneal metastasis from colorectal cancer (CARCINOSIS).****Summary**

EudraCT number	2015-002917-30
Trial protocol	AT
Global end of trial date	16 December 2019

Results information

Result version number	v1 (current)
This version publication date	05 September 2020
First version publication date	05 September 2020

Trial information**Trial identification**

Sponsor protocol code	CARCINOSIS
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Währinger Gürtel 18-20, Vienn, Austria, 1090
Public contact	Department of Surgery, Medical University of Vienna, 0043 14040056210, thomas.bachleitner-hofmann@meduniwien.ac.at
Scientific contact	Department of Surgery, Medical University of Vienna, 0043 14040056210, thomas.bachleitner-hofmann@meduniwien.ac.at

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	10 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2019
Global end of trial reached?	Yes
Global end of trial date	16 December 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to prospectively assess the histopathological response to neoadjuvant chemotherapy with FOLFOXIRI + bevacizumab in peritoneal tumor deposits of 30 patients with pcCRC by determining the % of viable tumor cells (vtc) in the resected specimen after neoadjuvant chemotherapy using standard pathology.

Protection of trial subjects:

For reasons of comprehensive view, in the following section a list of adverse events from a clinical trial investigating the FOLFOXIRI + Bevacizumab treatment regimen in patients with metastatic colorectal cancer is provided. The complete listings are included in the Summary of Product Characteristics of Fluorouracil Accord, rev. 02/2014, the Summary of Product Characteristics of Calciumfolinat "Ebewe", rev. 01/2015, the Summary of Product Characteristics of Irinotecan Fresenius, rev. 11/2013, the Summary of Product Characteristics of Oxaliplatin Accord, rev. 04/2012 and the Summary of Product Characteristics of Avastin, rev. 03/2015.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	3
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After signing the informed consent form all patients will be screened and baseline procedures performed from 28 days to 1 day prior to surgical exploration, Signed informed consent, Demographics and medical history, Concomitant medications, Physical examination, Vital signs, ECOG performance status, 12 lead ECG, Laboratory tests, Urinalysis, Tumor mar

Pre-assignment period milestones

Number of subjects started	8
Number of subjects completed	8

Period 1

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

Arms

Arm title	Assessment of histopathological response to combination chemot
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fluorouracil Accord
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous use

Dosage and administration details:

Fluorouracil is supplied as a clear, colourless liquid. The pH ranges from 8.6 -9.4. The formulation contains 50 mg Fluorouracil/1ml, sodium hydroxide, hydrochloric acid and water for injection (WFI).

Investigational medicinal product name	Calciumfolinat "Ebewe"
Investigational medicinal product code	
Other name	LEUCOVORIN CALCIUM
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous use

Dosage and administration details:

Leucovorin is supplied as a clear, colourless to slightly yellow liquid. The pH ranges from 6.5 – 8.5. The formulation contains 12.71 mg Calciumfolinat .5 H₂O (corresponding to 10 mg folinic acid) and water for injection (WFI).

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

Dosage and administration details:

Irinotecan is supplied as a clear, slightly yellow liquid. The formulation contains 20 mg Irinotecanhydrochloride-Trihydrate/1ml, sorbitol (E 420), lactic acid, sodium hydroxide, hydrochloric acid and water for injection (WFI).

Investigational medicinal product name	Oxaliplatin Accord
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intracavernous use

Dosage and administration details:

Oxaliplatin is supplied as a clear, colourless sterile liquid. The pH ranges from 3.5-6.5. The formulation contains 5mg Oxaliplatin/1ml, lactose-monohydrate and water for injection (WFI).

Investigational medicinal product name	AVASTIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab is supplied as a clear to slightly opalescent, colourless to pale brown, sterile liquid for intravenous infusion in single-use vials which are preservative-free. Bevacizumab will be supplied either in 5 mL (100 mg, 25 mg/ml) glass vials with a 4 ml fill, or in 20 ml (400 mg, 25 mg/ml) glass vials with a 16 ml fill. The formulation contains sodium phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI), USP.

Number of subjects in period 1	Assessment of histopathological response to combination chemot
Started	8
Completed	6
Not completed	2
Death	2

Baseline characteristics

Reporting groups

Reporting group title	Assessment of histopathological response to combination chemot
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Reporting group description: -

Reporting group values	Assessment of histopathological response to combination chemot	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	
From 65-84 years	5	5	
Gender categorical Units: Subjects			
Female	3	3	
Male	5	5	

Subject analysis sets

Subject analysis set title	Overall trial
Subject analysis set type	Full analysis

Subject analysis set description:

The primary objective of the study is to prospectively assess the histopathological response to neoadjuvant chemotherapy with FOLFOXIRI + bevacizumab in peritoneal tumor deposits of 30 patients with pCRC by determining the percentage of viable tumor cells in the resected specimen after neoadjuvant chemotherapy. For patients with multiple peritoneal specimens, the median percentage of viable cells in all specimens will be used. Patients with 0-49% of viable cells will be considered as responders. The timepoint of the assessment of the primary objective will be during re-exploratory surgery/surgical cytoreduction between days 78 and 106 of the treatment phase of the study. We hypothesize that there will be >30% responders after neoadjuvant chemotherapy with FOLFOXIRI + bevacizumab.

Reporting group values	Overall trial		
Number of subjects	8		
Age categorical Units: Subjects			
Adults (18-64 years)	3		
From 65-84 years	5		
Gender categorical Units: Subjects			
Female	3		
Male	5		

End points

End points reporting groups

Reporting group title	Assessment of histopathological response to combination chemot
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Reporting group description: -

Subject analysis set title	Overall trial
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Subject analysis set type	Full analysis
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Subject analysis set description:

The primary objective of the study is to prospectively assess the histopathological response to neoadjuvant chemotherapy with FOLFOXIRI + bevacizumab in peritoneal tumor deposits of 30 patients with pcCRC by determining the percentage of viable tumor cells in the resected specimen after neoadjuvant chemotherapy. For patients with multiple peritoneal specimens, the median percentage of viable cells in all specimens will be used. Patients with 0-49% of viable cells will be considered as responders. The timepoint of the assessment of the primary objective will be during re-exploratory surgery/surgical cytoreduction between days 78 and 106 of the treatment phase of the study. We hypothesize that there will be >30% responders after neoadjuvant chemotherapy with FOLFOXIRI + bevacizumab.

Primary: Histopathological response to chemotherapy with FOLFOXIRI + bevacizumab

End point title	Histopathological response to chemotherapy with FOLFOXIRI + bevacizumab ^[1]
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End point description:

End point type	Primary
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End point timeframe:

During Re-exploratory/surgical cytoreduction (3 to 5 weeks after completion of chemotherapy (days 78 to 106))

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: no comparison between arms. no statistical analysis performed due to premature termination.

End point values	Assessment of histopathological response to combination chemot			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: whole				
responder	5			
non-responder	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

31.3.2016 until 10.1.2019

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal necrosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urogenital infection bacterial			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Injury, poisoning and procedural complications			
Heat exhaustion			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Deep vein thrombosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nervous system disorders			
Speech disorder			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Polyneuropathy			

subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
General disorders and administration site conditions Malaise subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Eye disorders Ocular hypertension subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1 1 / 8 (12.50%) 2 1 / 8 (12.50%) 1 2 / 8 (25.00%) 2		
Skin and subcutaneous tissue disorders Photosensitivity reaction			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported