



## Clinical trial results:

### A randomized phase II of bevacizumab, capecitabine and radiation therapy with or without oxaliplatin in the preoperative treatment of locally advanced rectal cancer

#### Summary

EudraCT number	2007-007177-23
Trial protocol	BE
Global end of trial date	

#### Results information

Result version number	v1
This version publication date	03 August 2017
First version publication date	03 August 2017
Summary attachment (see zip file)	Synopsis from FSR (AXE Beam Final study report synopsis only.pdf) Consort chart (AXE Beam Final study report - consort chart.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	s51104
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00828672
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	UZLeuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Prof. Dr. Eric Van Cutsem, UZ Leuven, 0032 16 34 42 25, eric.vancutsem@uzleuven.be
Scientific contact	Prof. Dr. Eric Van Cutsem, UZ Leuven, 0032 16 34 42 25, eric.vancutsem@uzleuven.be

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	Interim
Date of interim/final analysis	20 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 April 2016
Global end of trial reached?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the activity of bevacizumab (Avastin) in combination with capecitabine (Xeloda) and radiation therapy with or without oxaliplatin (Eloxatin) in the pre-operative treatment of locally advanced rectal cancer, followed by TME resection, in a multicenter setting.

Protection of trial subjects:

Ethics review and approval, informed consent, prophylactic anti-emetic medication administered prior to oxaliplatin infusions in Arm A, dummy run for radiation therapy for appropriate treatment planning for each patient, supportive care and routine monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 84
Worldwide total number of subjects	84
EEA total number of subjects	84

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)	58
From 65 to 84 years	26
85 years and over	0

## Subject disposition

### Recruitment

#### Recruitment details:

Eighty-four patients were included. First patient enrolled: 22-Jun-2009. Last patient enrolled: 29-Sep-2013. Participating sites: UZ Leuven, Erasme Hospital Bruxelles, Cliniques Universitaires St-Luc Bruxelles, AZ St. Lucas Brugge, AZ Groeninge Kortrijk, CHU Sart-Tilman Liege, OLVZ Aalst, H. Hart Ziekenhuis Roeselare, Clinique Saint Elisabeth Namur

### Pre-assignment

#### Screening details:

Target population was represented by patients with locally advanced rectal cancer (tumour beyond mesorectal fascia (T4) or tumour  $\leq 2$  mm from mesorectal fascia or T3 tumour  $< 5$  cm from anal verge by MRI), histologically confirmed. Pts were screened as per incl and excl criteria per protocol. Screening failures were not recorded in the eCRF.

### Period 1

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

### Arms

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

#### Arm description:

Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

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

#### Dosage and administration details:

Dose, frequency & treatment mode: 5 mg/kg via a 1-hour IV infusion, on days 1, 15, 29 and 43, concurrently with radiotherapy. Bevacizumab administration precedes the oxaliplatin infusion in Arm A.

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

#### Dosage and administration details:

Dose, frequency & treatment mode (In Arm A only): 50 mg/m<sup>2</sup> via a 1-hour IV infusion, on days 15, 22, 29, 36 and 43, concurrently with radiotherapy.

Investigational medicinal product name	Xeloda
Investigational medicinal product code	
Other name	Capecitabine
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

#### Dosage and administration details:

Dose, frequency & treatment mode: twice-daily 825 mg/m<sup>2</sup> (equivalent to a total daily dose of 1650 mg/m<sup>2</sup>) days 15-47, 5 days per week, concurrently with radiotherapy.

<b>Arm title</b>	Arm B
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Arm description:

Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

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

Dosage and administration details:

Dose, frequency & treatment mode: 5 mg/kg via a 1-hour IV infusion, on days 1, 15, 29 and 43, concurrently with radiotherapy. Bevacizumab administration precedes the oxaliplatin infusion in Arm A.

Investigational medicinal product name	Xeloda
Investigational medicinal product code	
Other name	Capecitabine
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose, frequency & treatment mode: twice-daily 825 mg/m<sup>2</sup> (equivalent to a total daily dose of 1650 mg/m<sup>2</sup>) days 15-47, 5 days per week, concurrently with radiotherapy.

Number of subjects in period 1	Arm A	Arm B
Started	43	41
Treatment start	43	41
Completed	43	41

## Period 2

Period 2 title	Study treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

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

Dosage and administration details:

Dose, frequency & treatment mode: 5 mg/kg via a 1-hour IV infusion, on days 1, 15, 29 and 43, concurrently with radiotherapy. Bevacizumab administration precedes the oxaliplatin infusion in Arm A.

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

Dosage and administration details:

Dose, frequency & treatment mode (In Arm A only): 50 mg/m<sup>2</sup> via a 1-hour IV infusion, on days 15, 22, 29, 36 and 43, concurrently with radiotherapy.

Investigational medicinal product name	Xeloda
Investigational medicinal product code	
Other name	Capecitabine
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose, frequency & treatment mode: twice-daily 825 mg/m<sup>2</sup> (equivalent to a total daily dose of 1650 mg/m<sup>2</sup>) days 15-47, 5 days per week, concurrently with radiotherapy.

<b>Arm title</b>	Arm B
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Arm description:

Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

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

Dosage and administration details:

Dose, frequency & treatment mode: 5 mg/kg via a 1-hour IV infusion, on days 1, 15, 29 and 43, concurrently with radiotherapy. Bevacizumab administration precedes the oxaliplatin infusion in Arm A.

Investigational medicinal product name	Xeloda
Investigational medicinal product code	
Other name	Capecitabine
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose, frequency & treatment mode: twice-daily 825 mg/m<sup>2</sup> (equivalent to a total daily dose of 1650 mg/m<sup>2</sup>) days 15-47, 5 days per week, concurrently with radiotherapy.

Number of subjects in period 2	Arm A	Arm B
Started	43	41
Completion chemoradiotherapy	43	40
Surgery	41	39
Completed	41	39
Not completed	2	2
Adverse event, non-fatal	-	1

Clinical complete response, no surgery	1	1
Lost to follow-up, surgery off protocol	1	-

### Period 3

Period 3 title	Post-surgery (<30 days)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

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

Arm description:

Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

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

Dosage and administration details:

Dose, frequency & treatment mode: 5 mg/kg via a 1-hour IV infusion, on days 1, 15, 29 and 43, concurrently with radiotherapy. Bevacizumab administration precedes the oxaliplatin infusion in Arm A.

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

Dosage and administration details:

Dose, frequency & treatment mode (In Arm A only): 50 mg/m<sup>2</sup> via a 1-hour IV infusion, on days 15, 22, 29, 36 and 43, concurrently with radiotherapy.

Investigational medicinal product name	Xeloda
Investigational medicinal product code	
Other name	Capecitabine
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose, frequency & treatment mode: twice-daily 825 mg/m<sup>2</sup> (equivalent to a total daily dose of 1650 mg/m<sup>2</sup>) days 15-47, 5 days per week, concurrently with radiotherapy.

<b>Arm title</b>	Arm B
Arm description:	
Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Arm type	Active comparator

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

Dosage and administration details:

Dose, frequency & treatment mode: 5 mg/kg via a 1-hour IV infusion, on days 1, 15, 29 and 43, concurrently with radiotherapy. Bevacizumab administration precedes the oxaliplatin infusion in Arm A.

Investigational medicinal product name	Xeloda
Investigational medicinal product code	
Other name	Capecitabine
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose, frequency & treatment mode: twice-daily 825 mg/m<sup>2</sup> (equivalent to a total daily dose of 1650 mg/m<sup>2</sup>) days 15-47, 5 days per week, concurrently with radiotherapy.

Number of subjects in period 3	Arm A	Arm B
Started	41	39
Pathological central review	41	38
Completed	41	38
Not completed	0	1
Central review materials NA	-	1

#### Period 4

Period 4 title	Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

#### Arms

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

Arm description:

Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

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

Dosage and administration details:

Dose, frequency & treatment mode: 5 mg/kg via a 1-hour IV infusion, on days 1, 15, 29 and 43, concurrently with radiotherapy. Bevacizumab administration precedes the oxaliplatin infusion in Arm A.

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

Dosage and administration details:

Dose, frequency & treatment mode (In Arm A only): 50 mg/m<sup>2</sup> via a 1-hour IV infusion, on days 15, 22, 29, 36 and 43, concurrently with radiotherapy.

Investigational medicinal product name	Xeloda
Investigational medicinal product code	
Other name	Capecitabine
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose, frequency & treatment mode: twice-daily 825 mg/m<sup>2</sup> (equivalent to a total daily dose of 1650 mg/m<sup>2</sup>) days 15-47, 5 days per week, concurrently with radiotherapy.

<b>Arm title</b>	Arm B
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Arm description:

Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

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

Dosage and administration details:

Dose, frequency & treatment mode: 5 mg/kg via a 1-hour IV infusion, on days 1, 15, 29 and 43, concurrently with radiotherapy. Bevacizumab administration precedes the oxaliplatin infusion in Arm A.

Investigational medicinal product name	Xeloda
Investigational medicinal product code	
Other name	Capecitabine
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose, frequency & treatment mode: twice-daily 825 mg/m<sup>2</sup> (equivalent to a total daily dose of 1650 mg/m<sup>2</sup>) days 15-47, 5 days per week, concurrently with radiotherapy.

<b>Number of subjects in period 4</b>	Arm A	Arm B
Started	41	38
Completed	42	41

Joined	1	3
Toxicity during CRT, surgery off protocol, in FU	-	1
No central review materials, had surgery, in FU	-	1
Clinical CR, no surgery, in FU	1	1





## Baseline characteristics

### Reporting groups

Reporting group title	Arm A
Reporting group description: Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm B
Reporting group description: Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	

Reporting group values	Arm A	Arm B	Total
Number of subjects	43	41	84
Age categorical			
Units: Subjects			
Adults (18-64 years)	29	29	58
From 65-84 years	14	12	26
Age continuous			
Exact age value at start of treatment was considered. No split per age group was performed.			
Units: years			
median	61	59	
full range (min-max)	26 to 77	35 to 78	-
Gender categorical			
Units: Subjects			
Female	14	12	26
Male	29	29	58
ECOG PS			
PS – Performance status			
Units: Subjects			
PS=0	36	37	73
PS=1	7	4	11
Distance from tumour to anal verge (colonoscopy)			
Distance from tumour to anal verge in cm - measured by colonoscopy			
Units: Subjects			
<5cm	18	15	33
>= 5 cm	13	15	28
NA	12	11	23
Distance to CRM (MRI)			
Distance to circumferential margin - in mm - measured by MRI scan			
Units: Subjects			
0 mm	21	24	45
< 2mm	6	2	8
>= 2 mm	9	10	19
NA	7	5	12
Tumour stage			
Units: Subjects			
T2	2	2	4
T3	34	31	65
T4	7	8	15

Nodal stage			
Units: Subjects			
N0	7	5	12
N1	15	18	33
N2	20	17	37
Nx	1	1	2

### Subject analysis sets

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

Subject analysis set description:

All patients that were randomized. In this study ITT set = per protocol (all patients that started treatment per protocol) = safety population (started treatment and had at least one dose)

Subject analysis set title	Efficacy set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients with pathologic assessment of microscopic preoperative response (patients in whom preoperative chemoradiotherapy was completed and surgical resection was performed as per protocol).

Subject analysis set title	Centrally reviewed efficacy set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients with pathologic assessment of microscopic preoperative response that was centrally reviewed (patients with post-surgical materials available for central review)

Reporting group values	Intent to treat	Efficacy set	Centrally reviewed efficacy set
Number of subjects	84	80	79
Age categorical			
Units: Subjects			
Adults (18-64 years)	58		
From 65-84 years	26		
Age continuous			
Exact age value at start of treatment was considered. No split per age group was performed.			
Units: years			
median	60		
full range (min-max)	26 to 78		
Gender categorical			
Units: Subjects			
Female	26		
Male	58		
ECOG PS			
PS – Performance status			
Units: Subjects			
PS=0	73		
PS=1	11		
Distance from tumour to anal verge (colonoscopy)			
Distance from tumour to anal verge in cm - measured by colonoscopy			
Units: Subjects			
<5cm	33		
>= 5 cm	28		
NA	23		

Distance to CRM (MRI)			
Distance to circumferential margin - in mm - measured by MRI scan			
Units: Subjects			
0 mm	45		
< 2mm	8		
>= 2 mm	19		
NA	12		
Tumour stage			
Units: Subjects			
T2	4		
T3	65		
T4	15		
Nodal stage			
Units: Subjects			
N0	12		
N1	33		
N2	37		
Nx	2		

## End points

### End points reporting groups

Reporting group title	Arm A
Reporting group description: Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm B
Reporting group description: Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm A
Reporting group description: Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm B
Reporting group description: Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm A
Reporting group description: Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm B
Reporting group description: Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm A
Reporting group description: Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm B
Reporting group description: Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm A
Reporting group description: Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Reporting group title	Arm B
Reporting group description: Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).	
Subject analysis set title	Intent to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients that were randomized. In this study ITT set = per protocol (all patients that started treatment per protocol) = safety population (started treatment and had at least one dose)	
Subject analysis set title	Efficacy set
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients with pathologic assessment of microscopic preoperative response (patients in whom preoperative chemoradiotherapy was completed and surgical resection was performed as per protocol).	
Subject analysis set title	Centrally reviewed efficacy set
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients with pathologic assessment of microscopic preoperative response that was centrally reviewed (patients with post-surgical materials available for central review)	

### Primary: Pathologic complete response (pCR) rate

End point title	Pathologic complete response (pCR) rate
End point description: Pathologic complete response (ypT0N0) was concluded if the pathologist was unable to demonstrate any intact viable cancer cells within the operative specimen. The presence of mucin lakes without associated adjacent malignant cells could be defined as a pathologic complete response. Histopathologic assessments of tumour response post chemoradiotherapy provided by the investigators (as read by local pathologists) were reviewed centrally for all patients for whom surgical materials were available. The diagnosis of independent central reviewers primed.	

End point type	Primary
End point timeframe:	
Post-surgery	

End point values	Arm A	Arm B	Centrally reviewed efficacy set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	41	38	79	
Units: Number of patients				
Dworak TRG=4 (Complete Response, no tumour left)	14	4	18	
Dworak TRG=3-4 (good tumour regression)	17	9	26	
Dworak TRG=0-1-2 (no or little tumour regression)	24	29	53	

<b>Attachments (see zip file)</b>	Tumour regression - main endpoint ypCR/AXE BEAM_main
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## Statistical analyses

<b>Statistical analysis title</b>	Counts of pathological complete response
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Statistical analysis description:

Descriptive. Counts of pathological complete response. Proportions with confidence intervals were calculated per arm. No formal statistical comparison between arms was performed. Detailed data available upon request.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
P-value	= 1 [1]
Method	Descriptive. No comparison

Notes:

[1] - This is a fictive value. P-value is not applicable. There is no comparison between arms.

## Secondary: Histopathologic R0 resection rate (negative resection margins)

End point title	Histopathologic R0 resection rate (negative resection margins)
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End point description:

Histopathologic R0 resection rate was defined as margins histologically negative for tumour involvement after resection. The circumferential resection margin (CRM) is considered to be involved if microscopic tumour is present <1mm from or at the inked circumferential or radial resection margin (51). Data on quality of mesorectal excision were expected but not collected consistently.

End point type	Secondary
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End point timeframe:

Post-surgery

End point values	Arm A	Arm B	Efficacy set	Centrally reviewed efficacy set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	41	39 <sup>[2]</sup>	80	75
Units: Number of cases				
Negative resection margins	40	37	78	71
Positive resection margins	1	2	2	4

Notes:

[2] - Pt that discontinued due to major toxicity and had surgery off protocol counted here as well

## Statistical analyses

Statistical analysis title	Counts of patients with negative resection margins
Statistical analysis description:	
Descriptive. Counts of patients with negative resection margins in centrally reviewed efficacy set. Proportions with confidence intervals were calculated per arm. No formal statistical comparison between arms was performed. Detailed data available upon request.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	= 1 <sup>[4]</sup>
Method	Descriptive. No comparison

Notes:

[3] - Descriptive

[4] - This is a fictive value. P-value is not applicable. There is no comparison between arms.

## Secondary: Pathologic downstaging rate and tumour regression rate

End point title	Pathologic downstaging rate and tumour regression rate
End point description:	
Pathologic tumour response was assessed according to the TNM staging system and according to the grading system for tumour regression as described by Dworak.	
Grade 0: no regression	
Grade 1: dominant tumour mass with obvious fibrosis and/or vasculopathy	
Grade 2: dominantly fibrotic changes with few tumour cells or groups (easy to find)	
Grade 3: very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucous substance	
Grade 4: no tumour cells, only a fibrotic mass (total regression or complete response)	
End point type	Secondary
End point timeframe:	
Post-surgery	

End point values	Arm A	Arm B	Centrally reviewed efficacy set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	41	38	79	
Units: Number of patients				
Dworak TRG 4 (complete response, no tumor left)	14	4	18	
Dworak TRG 3-4 (good tumor regression)	17	9	26	

Dworak TRG 0-1-2 (no or little tumor regression)	24	29	53	
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## Statistical analyses

<b>Statistical analysis title</b>	Counts of tumour regression grades
Statistical analysis description:	
Descriptive. Counts of patients with different tumour regression grades after treatment. Proportions with confidence intervals were calculated per arm. No formal statistical comparison between arms was performed. Detailed data available upon request.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other <sup>[5]</sup>
P-value	= 1 <sup>[6]</sup>
Method	Descriptive. No comparison

Notes:

[5] - Descriptive

[6] - This is a fictive value. P-value is not applicable. There is no comparison between arms.

## Secondary: Clinical response rate

<b>End point title</b>	Clinical response rate
End point description:	
Baseline measurements were performed within 4 weeks prior to treatment start. The same methods of assessment (CT and/or MRI) and the same techniques were used for each measurable lesion, identified at baseline and during follow-up.	
<ul style="list-style-type: none"> <li>Complete Response (CR) is disappearance of all clinical and radiological evidence of tumour (both target and non-target lesions).</li> <li>Partial Response (PR) is at least a 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum LD.</li> <li>Stable Disease (SD) is steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.</li> <li>Progressive Disease (PD) is at least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute progressive disease. In exceptional circumstances, unequivocal progression of non-target lesions may be accepted as evidence of disease progressi</li> </ul>	
End point type	Secondary
End point timeframe:	
Pre-surgery	

<b>End point values</b>	Arm A	Arm B	Intent to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	41	84	
Units: Number of patients				
CR	3	5	8	
PR	24	17	41	
SD	9	13	22	
PD	0	1	1	
NA	7	5	12	



## Statistical analyses

<b>Statistical analysis title</b>	Counts of clinical response
Statistical analysis description: Descriptive. Counts of clinical response. Rates of different types of response (CRR; OR; DCR) with confidence intervals were calculated per arm. No formal statistical comparison between arms was performed. Detailed data available upon request.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other <sup>[7]</sup>
P-value	= 1 <sup>[8]</sup>
Method	Descriptive. No comparison

Notes:

[7] - Descriptive

[8] - This is a fictive value. P-value is not applicable. There is no comparison between arms.

## Secondary: Disease status (recurrence)

End point title	Disease status (recurrence)
End point description: Recurrence of disease (local or distant) and disease free survival at 3 and 5 years	
End point type	Secondary
End point timeframe: Post-treatment + 5 years	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: Number of patients				
Recurred	9	8		
Not recurred	33	33		
Lost to follow-up	0	0		

## Statistical analyses

<b>Statistical analysis title</b>	Counts of disease recurrence
Statistical analysis description: 1. Counts of patients with disease recurrence. Proportions with confidence intervals were calculated per arm. No formal statistical comparison between arms was performed. Detailed data available upon request.	

2. Kaplan-Meier survival analysis (median disease free survival time not yet reached as of 20-Feb-2017)  
Analysis to be redone at 5 years post study (expected March 2019)

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other <sup>[9]</sup>
P-value	= 1 <sup>[10]</sup>
Method	Descriptive. No comparison

Notes:

[9] - Kaplan-Meier

[10] - This is a fictive value. P-value is not applicable. There is no comparison between arms.

## Secondary: Survival

End point title	Survival
End point description: Deaths and overall survival at 3 and 5 years.	
End point type	Secondary
End point timeframe: Post treatment + 5 years	

End point values	Arm A	Arm B	Intent to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	41	84	
Units: Number of patients				
Deceased	4	5	9	
Alive	38	36	74	
Lost to FU	0	0	1	

## Statistical analyses

Statistical analysis title	Counts of patients deceased
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Statistical analysis description:

1. Counts of patients deceased. Proportions with confidence intervals were calculated per arm. No formal statistical comparison between arms was performed. Detailed data available upon request.

2. Kaplan-Meier survival analysis (median overall survival time not yet reached as of 20-Feb-2017)  
Analysis to be redone at 5 years post study (expected March 2019)

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other <sup>[11]</sup>
P-value	= 1 <sup>[12]</sup>
Method	Descriptive. No comparison

Notes:

[11] - Kaplan-Meier

[12] - This is a fictive value. P-value is not applicable. There is no comparison between arms.

## Secondary: Safety

End point title	Safety
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End point description:

Adverse events graded as per NCI CTCAE (US National Cancer Institute Common Terminology Criteria for Adverse Events) version 3.0

All Serious Adverse Events occurrences are reported; all Adverse Events related and not related to study treatment are reported; all severe laboratory events (hematology and biochemistry Gr 3 and higher) are reported; all severe postoperative complications (Gr 3 and higher) occurred within the first month post surgery are reported.

End point type	Secondary
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End point timeframe:

All safety events (serious and non serious) from signature of informed consent to +30 days after surgery

End point values	Arm A	Arm B	Intent to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	41	84	
Units: Number of cases and rates				
Serious Adverse Events	22	12	34	
Non Serious Adverse Events	564	426	990	
Severe lab events	27	16	43	
Postoperative complications at 1 month	14	9	23	

## Statistical analyses

Statistical analysis title	Counts of safety events
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Statistical analysis description:

Descriptive. Counts of safety events. Proportions with confidence intervals were calculated per arm. No formal statistical comparison between arms was performed. Detailed data available upon request.

Comparison groups	Arm A v Arm B
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Number of subjects included in analysis	84
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Analysis specification	Pre-specified
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Analysis type	other <sup>[13]</sup>
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P-value	= 1 <sup>[14]</sup>
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Method	Descriptive. No comparison
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Notes:

[13] - No comparison was performed between arms. Descriptive statistics only.

[14] - This is a fictive value. P-value is not applicable. There is no comparison between arms.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signature of ICF to 30 days post surgery with follow-up for residual toxicity after this period if applicable

Adverse event reporting additional description:

All SAE occurrences are reported and displayed below.

Only Gr 3-4-5 non-serious adverse events are reported in this database.

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI CTC AE
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Dictionary version	3
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### Reporting groups

Reporting group title	Arm A
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Reporting group description:

Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

Reporting group title	Arm B
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Reporting group description:

Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 43 (48.84%)	12 / 41 (29.27%)	
number of deaths (all causes)	4	5	
number of deaths resulting from adverse events	0	1	
Vascular disorders			
Lung embolism	Additional description: Lung embolism Gr 5 Postoperative		
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Neuropathy motor	Additional description: Neuropathy, motor (cranial, palate, pharynx) Gr 3 (swallowing problems) During chemoradiotherapy		
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure	Additional description: Seizure Gr 2 in a patient with epileptic background During chemoradiotherapy		

subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever	Additional description: Fever Gr 1 During chemoradiotherapy		
subjects affected / exposed	3 / 43 (6.98%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal haemorrhage	Additional description: Rectal haemorrhage Gr 2 following rectal biopsy During chemoradiotherapy		
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhea Gr 3 During chemoradiotherapy		
subjects affected / exposed	3 / 43 (6.98%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula	Additional description: Rectovaginal fistula Gr 2 Postoperative		
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leak	Additional description: Anastomotic leak Gr 3 ; 2 in arm A and 3 in arm B - all events also SAE Timepoint of onset = Postoperative		
subjects affected / exposed	2 / 43 (4.65%)	3 / 41 (7.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction	Additional description: Obstruction GI Gr 2 and Gr 3, both in arm A Postoperative		
subjects affected / exposed	2 / 43 (4.65%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presacral hematoma	Additional description: Presacral hematoma Gr 2 Postoperative		

subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression	Additional description: Depression Gr 3 During chemoradiotherapy		
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia	Additional description: Febrile neutropenia Gr 3 During chemoradiotherapy		
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock	Additional description: Catheter related infection Gr 4 During chemoradiotherapy		
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: 2 Urinary tract infection Gr 2 (1 in each arm) and 1 Urinary tract infection Gr 3 in arm A During chemoradiotherapy		
subjects affected / exposed	2 / 43 (4.65%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection	Additional description: Catheter site infection Gr 3 with positive hemocultures Postoperative		
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection	Additional description: 5 peri-anal wound infections Gr 3 (4 in arm A; 1 in arm B) ; 1 wound infection with evisceration Gr 4 in arm A; 1 Gr 5 wound infection in a patient with tumor break during surgery in arm B		
subjects affected / exposed	5 / 43 (11.63%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	1 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 43 (41.86%)	15 / 41 (36.59%)	
Vascular disorders			
Deep venous thrombosis	Additional description: DVT Gr 3 Timepoint of onset = Postoperative		
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Embolism	Additional description: Embolism Gr 4 and embolism Gr 5 both in arm B		
subjects affected / exposed	0 / 43 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue Gr 3 (2 pts in arm A and 1 pt in arm B - also an SAE for this pt) Timepoint of onset = during chemoradiotherapy		
subjects affected / exposed	2 / 43 (4.65%)	1 / 41 (2.44%)	
occurrences (all)	2	1	
Sweating	Additional description: Sweating Gr 3 Timepoint of onset = Postoperative		
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pain pulmonary/respiratory	Additional description: Sore throat Gr 3 and laryngeal pain Gr 3 in one patient in arm B Timepoint of onset = Follow up post end of treatment visit		
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	2	
Psychiatric disorders			
Depression	Additional description: Depression Gr 3 - also an SAE Timepoint of onset - during chemoradiotherapy		
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Cardiac disorders			
Hypertension baseline	Additional description: Hypertension Gr 3 Timepoint of onset = baseline		
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Hypertension	Additional description: Hypertension Gr 3 in 2 pts in arm B Timepoint of onset = during chemoradiotherapy		
subjects affected / exposed	0 / 43 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Cardiopulmonary arrest	Additional description: Cardiopulmonary arrest Gr 5 Timepoint of onset = Follow up post end of treatment visit		

subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 41 (2.44%) 1	
Nervous system disorders			
Neuropathy sensory	Additional description: Neuropathy sensory Gr 3 Timepoint of onset - during chemoradiotherapy		
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 41 (0.00%) 0	
Syncope	Additional description: Syncope Gr 3 Timepoint of onset - during chemoradiotherapy		
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 41 (0.00%) 0	
Neuropathy - cranial	Additional description: Neuropathy - cranial Gr 3 (also an SAE) Timepoint of onset = Follow up post end of treatment visit		
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 41 (2.44%) 1	
Blood and lymphatic system disorders			
Platelet count decreased	Additional description: Platelet count decreased Gr 3 Timepoint of onset = during chemoradiotherapy		
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 2	0 / 41 (0.00%) 0	
Disseminated Intravascular Coagulation	Additional description: Disseminated Intravascular Coagulation Gr3 Timepoint of onset = during chemoradiotherapy		
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 41 (0.00%) 0	
Haemorrhage	Additional description: Hemorrhage with surgery Gr 3 Timepoint of onset = during chemoradiotherapy		
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 41 (2.44%) 1	
Hematoma postoperative	Additional description: Hematoma Gr 3 in 1 pt in arm B (also SAE) Timepoint of onset = postoperative		
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 41 (2.44%) 1	
Hematoma	Additional description: Hematoma Gr 3 (also an SAE) Timepoint of onset = Follow up post end of treatment visit		
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 41 (2.44%) 1	
Ear and labyrinth disorders			
Meniere's disease	Additional description: Pt with baseline Meniere's disease Gr3 (since 1999) Timepoint of onset = baseline		
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 41 (0.00%) 0	
Gastrointestinal disorders			



Anorexia	Additional description: Anorexia Gr 3	
	1 / 43 (2.33%)	0 / 41 (0.00%)
subjects affected / exposed	1	0
occurrences (all)		
Diarrhea	Additional description: Diarrhea Gr 3 in 4 pts in arm A (three episodes were an SAE) Timepoint of onset - during chemoradiotherapy	
	4 / 43 (9.30%)	0 / 41 (0.00%)
subjects affected / exposed	4	0
occurrences (all)		
Anal pain	Additional description: Pain gastro-intestinal - anal pain Gr 3 Timepoint of onset - during chemoradiotherapy	
	0 / 43 (0.00%)	1 / 41 (2.44%)
subjects affected / exposed	0	1
occurrences (all)		
Leak GI	Additional description: Leak GI Gr 3 Timepoint of onset = Postoperative	
	2 / 43 (4.65%)	3 / 41 (7.32%)
subjects affected / exposed	2	3
occurrences (all)		
Obstruction GI	Additional description: Onstruction GI Gr 3 in 2 pts in arm A (for 1 also an SAE) and in 1 pt in arm B (also an SAE) Timepoint of onset = Postoperative	
	2 / 43 (4.65%)	1 / 41 (2.44%)
subjects affected / exposed	2	1
occurrences (all)		
Pain GI	Additional description: Stomach pain Gr 3 and pain due to leak Gr 3 Timepoint of onset = Postoperative	
	2 / 43 (4.65%)	0 / 41 (0.00%)
subjects affected / exposed	2	0
occurrences (all)		
Discharge from the anus	Additional description: Purulent discharge from the anus Gr 3 Timepoint of onset = postoperative	
	0 / 43 (0.00%)	1 / 41 (2.44%)
subjects affected / exposed	0	1
occurrences (all)		
Ascites	Additional description: Ascites Gr 5 Timepoint of onset = Follow up post end of treatment visit	
	0 / 43 (0.00%)	1 / 41 (2.44%)
subjects affected / exposed	0	1
occurrences (all)		
Dysphagia	Additional description: Dysphagia Gr 3 Timepoint of onset = Follow up post end of treatment visit	
	0 / 43 (0.00%)	1 / 41 (2.44%)
subjects affected / exposed	0	1
occurrences (all)		
Skin and subcutaneous tissue disorders		
Dermatitis	Additional description: Dermatitis associated with radiotherapy Gr 3 Timepoint of onset = during chemoradiotherapy	
	1 / 43 (2.33%)	3 / 41 (7.32%)
subjects affected / exposed	1	3
occurrences (all)		
Rash	Additional description: Rash Gr 3 Timepoint of onset = during chemoradiotherapy	

subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 41 (2.44%) 1	
Renal and urinary disorders Leak, GU	Additional description: Leak, GU Gr 5 Timepoint of onset = postoperative		
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 41 (2.44%) 1	
Musculoskeletal and connective tissue disorders Pain muskuloskeletal	Additional description: Pain muskuloskeletal Gr 3 Timepoint of onset = Postoperative		
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 41 (0.00%) 0	
Infections and infestations Febrile neutropenia	Additional description: Febrile neutropenia Gr 3 (also an SAE) Timepoint of onset = during chemoradiotherapy		
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 41 (0.00%) 0	
Catheter site infection	Additional description: Catheter site infection Gr 3 (also an SAE) Timepoint of onset = during chemoradiotherapy		
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 41 (0.00%) 0	
Sepsis	Additional description: Sepsis Gr 3 and septic shock Gr 4 Timepoint of onset = during chemoradiotherapy		
subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	0 / 41 (0.00%) 0	
Wound infection	Additional description: 5 peri-anal wound infections Gr 3 (4 in arm A; 1 in arm B) ; 1 wound infection with evisceration Gr 4 in arm A; 1 Gr 5 wound infection in a patient with tumor break during surgery in arm B Timepoint of onset : postoperative and follow-up		
subjects affected / exposed occurrences (all)	5 / 43 (11.63%) 5	2 / 41 (4.88%) 2	
Peritonitis	Additional description: Peritonitis Gr 5 (tumor break during surgery) - part of SAE Timepoint of onset = follow-up		
subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 41 (2.44%) 1	
Infection due to leak of anastomosis	Additional description: Infection due to leak of anastomosis Gr 3 (part of an SAE) Timepoint of onset = follow-up		
subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 41 (0.00%) 0	
Metabolism and nutrition disorders Hypocalcemia	Additional description: Hypocalcemia Gr 3 Timepoint of onset - during chemoradiotherapy		

subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Hypokalemia	Additional description: Hypokalemia Gr 3 Timepoint of onset - during chemoradiotherapy		
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Hyponatremia	Additional description: Hyponatremia Gr 3 Timepoint of onset = Postoperative		
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2011	The amendment consisted mainly in corrections and clarifications of the procedures. The Informed Consent form was not changed.
07 December 2011	The amendment consisted mainly in changes regarding the investigational capecitabine (declaration of change of drug production site). The Informed Consent Form was not changed.

Notes:

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### 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.

The study was not powered to allow for formal statistical comparisons between arms. Descriptive statistics only.

Use of a surrogate main endpoint (pCR rate) instead of clinical efficacy end-points

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25867261>

<http://www.ncbi.nlm.nih.gov/pubmed/23997939>

<http://www.ncbi.nlm.nih.gov/pubmed/24876730>