



Clinical trial results:

CAO/ARO/AIO-12: Induction chemotherapy before or after preoperative chemoradiotherapy and surgery for locally advanced rectal cancer: A randomized phase II trial of the German Rectal Cancer Study Group

Summary

EudraCT number	2011-006310-13
Trial protocol	DE
Global end of trial date	16 June 2023

Results information

Result version number	v1 (current)
This version publication date	11 March 2024
First version publication date	11 March 2024

Trial information

Trial identification

Sponsor protocol code	CAO/ARO/AIO-12
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02363374
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Goethe University
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt, Germany,
Public contact	Dept. of Radiation Therapy and Oncology, Studiensekretariat, Goethe University Frankfurt, 0049 06963014655,
Scientific contact	Dept. of Radiation Therapy and Oncology, Studiensekretariat, Goethe University Frankfurt, 0049 06963014655,

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	16 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2023
Global end of trial reached?	Yes
Global end of trial date	16 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the efficacy of induction chemotherapy followed by chemoradiotherapy, or the other way round, before surgery in patients with locally advanced rectal cancer. As primary endpoint, the rate of patients with pathological complete remissions (pCR) will be compared exploratively between the treatment arms and to expectations derived from historical data.

Protection of trial subjects:

A Data Safety and Monitoring Board with at least three members will be established, consisting of experts in medical, surgical or radiotherapeutic oncology specializing in rectal cancer, and a statistical expert.

The DSMB will receive regular information on safety results of the trial, namely a list of reported SAEs/SUSARs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2014
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?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 311
Worldwide total number of subjects	311
EEA total number of subjects	311

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)	194
From 65 to 84 years	117
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female patients with histologically confirmed diagnosis of rectal adenocarcinoma localised 0 – 12 cm from the anocutaneous line as measured by rigid rectoscopy (i.e. lower and middle third of the rectum)

Pre-assignment

Screening details:

Patients diagnosed with rectal cancer have been screened

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control arm A

Arm description:

The therapy starts with three induction chemotherapy cycles (Folinic acid: 400 mg/m², 2h-civ Oxaliplatin: 100 mg/m², 2h-civ, 5-FU: 2400 mg/m², 46h-civ) followed by chemoradiotherapy (Radiotherapy: 28 x 1.8 Gy; total 50.4 Gy, 5 fractions per week, 5-FU: 250 mg/m² per day, civ, on day 1-14, day 22-35 of radiotherapy, Oxaliplatin: 50 mg/m², day 1, 8, 22, and 29 of radiotherapy) Accordingly, chemoradiotherapy should be finalized on day 81, if no delays are required. Surgery should be performed about 6 weeks later, i.e. around day 123.

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

Dosage and administration details:

Oxaliplatin: 100 mg/m², 2h-civ on day 1, 15 and 29 + 50 mg/m², day 1, 8, 22, and 29 of radiotherapy, total 500 mg/m²

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

Dosage and administration details:

2400 mg/m², 46h-civ on day 1, 15 and 29 + 250 mg/m² per day, civ, on day 1-14, day 22-35 of radiotherapy, total 14200 mg/m²

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

Dosage and administration details:

400 mg/m², 2h-civ on day 1, 15 and 29, total 1200 mg/m²

Arm title	Experimental arm B
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Arm description:

The therapy starts with chemoradiotherapy (Radiotherapy: 28 x 1.8 Gy; total 50.4 Gy, 5 fractions per week, 5-FU: 250 mg/m² per day, civ, on day 1-14, day 22-35 of radiotherapy, Oxaliplatin: 50 mg/m², day 1, 8, 22, and 29 of radiotherapy) followed by three chemotherapy cycles (Folinic acid: 400 mg/m², 2h-civ

Oxaliplatin: 100 mg/m², 2h-civ, 5-FU: 2400 mg/m², 46h-civ).

Surgery should be performed about 6 weeks later, i.e. around day 123.

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

Dosage and administration details:

Oxaliplatin: 50 mg/m², day 1, 8, 22, and 29 of radiotherapy + 100 mg/m², 2h-civ on day on day 57, 71 and 85, total 500 mg/m²

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

Dosage and administration details:

250 mg/m² per day, civ, on day 1-14, day 22-35 of radiotherapy+ 2400 mg/m², 46h-civ on day 57, 71 and 85, total 14200 mg/m²

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

Dosage and administration details:

400 mg/m², 2h-civ on day 1, 15 and 29, total 1200 mg/m²

Number of subjects in period 1^[1]	Control arm A	Experimental arm B
Started	156	150
Completed	142	142
Not completed	14	8
Adverse event, serious fatal	1	1
refused because of cCR	6	4
unknown	1	2
refused because of other reason	-	1
No matching reasons found	4	-
Lack of efficacy	2	-

Notes:

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

Justification: 311 patients were randomized but 5 patients were excluded because of constant withdrawal or protocol entry violation. All further analyses were performed within the 306 patients.

[<https://doi.org/10.1200/JCO.19.00308>]

Baseline characteristics

Reporting groups

Reporting group title	Control arm A
Reporting group description:	
The therapy starts with three induction chemotherapy cycles (Folinic acid: 400 mg/m ² , 2h-civ Oxaliplatin: 100 mg/m ² , 2h-civ, 5-FU: 2400 mg/m ² , 46h-civ) followed by chemoradiotherapy (Radiotherapy: 28 x 1.8 Gy; total 50.4 Gy, 5 fractions per week, 5-FU: 250 mg/m ² per day, civ, on day 1-14, day 22-35 of radiotherapy, Oxaliplatin: 50 mg/m ² , day 1, 8, 22, and 29 of radiotherapy) Accordingly, chemoradiotherapy should be finalized on day 81, if no delays are required. Surgery should be performed about 6 weeks later, i.e. around day 123.	
Reporting group title	Experimental arm B
Reporting group description:	
The therapy starts with chemoradiotherapy (Radiotherapy: 28 x 1.8 Gy; total 50.4 Gy, 5 fractions per week, 5-FU: 250 mg/m ² per day, civ, on day 1-14, day 22-35 of radiotherapy, Oxaliplatin: 50 mg/m ² , day 1, 8, 22, and 29 of radiotherapy) followed by three chemotherapy cycles (Folinic acid: 400 mg/m ² , 2h-civ Oxaliplatin: 100 mg/m ² , 2h-civ, 5-FU: 2400 mg/m ² , 46h-civ). Surgery should be performed about 6 weeks later, i.e. around day 123.	

Reporting group values	Control arm A	Experimental arm B	Total
Number of subjects	156	150	306
Age categorical			
Units: Subjects			
Adults (18-64 years)	103	91	194
From 65-84 years	53	59	112
Age continuous			
Units: years			
median	62	61	
full range (min-max)	19 to 79	39 to 81	-
Gender categorical			
Units: Subjects			
Female	50	50	100
Male	106	100	206
ECOG			
Units: Subjects			
ECOG 0	118	100	218
ECOG 1	32	48	80
Missing	6	2	8
clinical tumor category			
Units: Subjects			
cT2	6	4	10
cT3	132	118	250
cT4	18	27	45
missing	0	1	1
clinical node stage			
Units: Subjects			
cN0	16	14	30
cN1-2	134	135	269
missing	6	1	7
clinical disease stage			

Units: Subjects			
Stage II	16	14	30
Stage III	134	135	269
missing	6	1	7
Distance of tumor to mesorectal fascia			
Units: Subjects			
less or equal 1mm	48	33	81
more than 1mm	108	117	225
Missing	0	0	0
Location from anal verge, cm			
Units: Subjects			
0-5	64	62	126
6-10	67	73	140
11 or higher	15	11	26
missing	10	4	14
Histology			
Units: Subjects			
Adenocarcinoma	152	143	295
Mucinous adenocarcinoma	1	5	6
Singet-ring cell adenocarcinoma	1	0	1
other	2	2	4
Tumor differentiation			
Units: Subjects			
Well	6	12	18
moderately	125	113	238
poorly	11	8	19
missing	14	17	31

Subject analysis sets

Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
306 patients, five excluded because withdrawal of consent or protocol entry violation	

Reporting group values	Intention to treat		
Number of subjects	306		
Age categorical			
Units: Subjects			
Adults (18-64 years)	194		
From 65-84 years	112		
Age continuous			
Units: years			
median	61		
full range (min-max)	19 to 81		
Gender categorical			
Units: Subjects			
Female	100		
Male	206		

ECOG			
Units: Subjects			
ECOG 0	218		
ECOG 1	80		
Missing	8		
clinical tumor category			
Units: Subjects			
cT2	10		
cT3	250		
cT4	45		
missing	1		
clinical node stage			
Units: Subjects			
cN0	30		
cN1-2	269		
missing	7		
clinical disease stage			
Units: Subjects			
Stage II	30		
Stage III	269		
missing	7		
Distance of tumor to mesorectal fascia			
Units: Subjects			
less or equal 1mm	81		
more than 1mm	225		
Missing	0		
Location from anal verge, cm			
Units: Subjects			
0-5	126		
6-10	140		
11 or higher	26		
missing	14		
Histology			
Units: Subjects			
Adenocarcinoma	295		
Mucinous adenocarcinoma	6		
Singet-ring cell adenocarcinoma	1		
other	4		
Tumor differentiation			
Units: Subjects			
Well	18		
moderatly	238		
poorly	19		
missing	31		

End points

End points reporting groups

Reporting group title	Control arm A
Reporting group description: The therapy starts with three induction chemotherapy cycles (Folinic acid: 400 mg/m ² , 2h-civ Oxaliplatin: 100 mg/m ² , 2h-civ, 5-FU: 2400 mg/m ² , 46h-civ) followed by chemoradiotherapy (Radiotherapy: 28 x 1.8 Gy; total 50.4 Gy, 5 fractions per week, 5-FU: 250 mg/m ² per day, civ, on day 1-14, day 22-35 of radiotherapy, Oxaliplatin: 50 mg/m ² , day 1, 8, 22, and 29 of radiotherapy) Accordingly, chemoradiotherapy should be finalized on day 81, if no delays are required. Surgery should be performed about 6 weeks later, i.e. around day 123.	
Reporting group title	Experimental arm B
Reporting group description: The therapy starts with chemoradiotherapy (Radiotherapy: 28 x 1.8 Gy; total 50.4 Gy, 5 fractions per week, 5-FU: 250 mg/m ² per day, civ, on day 1-14, day 22-35 of radiotherapy, Oxaliplatin: 50 mg/m ² , day 1, 8, 22, and 29 of radiotherapy) followed by three chemotherapy cycles (Folinic acid: 400 mg/m ² , 2h-civ Oxaliplatin: 100 mg/m ² , 2h-civ, 5-FU: 2400 mg/m ² , 46h-civ). Surgery should be performed about 6 weeks later, i.e. around day 123.	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: 306 patients, five excluded because withdrawal of consent or protocol entry violation	

Primary: Pathological complete response

End point title	Pathological complete response ^[1]
End point description: The primary end point, pathologic complete response (pCR), was defined as ypT0N0 after surgery.	
End point type	Primary
End point timeframe: Start of treatment up to surgery	

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: The statistical procedure is described in detail in the original publication, <https://doi.org/10.1200/JCO.19.0030>.

It is too complex to add the analysis methods within this system.

End point values	Control arm A	Experimental arm B	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	156	150	306	
Units: Patients	27	38	65	

Statistical analyses

No statistical analyses for this end point

Secondary: 3-year disease-free survival

End point title	3-year disease-free survival
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End point description:

Regarding the definition of secondary endpoints, DFS was defined as the time between randomization and either macroscopically visible gross tumor after surgery (R2 resection), no resection due to tumor progression, locoregional recurrence after R0/1 resection of the primary tumor, distant metastases, or death from any cause, whichever occurred first; a local regrowth in patients with cCR and NOM was censored if salvage surgery resulted in a R0/1 resection, as recently recommended.

End point type	Secondary
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End point timeframe:

Time from randomization to any event listed below.

End point values	Control arm A	Experimental arm B	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	156	150	306	
Units: Events	46	43	89	

Statistical analyses

Statistical analysis title	Cox regression
Comparison groups	Experimental arm B v Control arm A
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.45
Variability estimate	Standard deviation

Secondary: 3-year cumulative incidence of locoregional recurrence

End point title	3-year cumulative incidence of locoregional recurrence
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End point description:

The cumulative incidence of locoregional recurrence and distant metastases was defined as the time between randomization and occurrence of any locoregional recurrence (after R0/1 resection of the primary tumor) and distant metastases, respectively, irrespective of whether this was a first event or not.

End point type	Secondary
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End point timeframe:

Time from randomization to event listed below.

End point values	Control arm A	Experimental arm B	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	156	150	306	
Units: Events	9	7	16	

Statistical analyses

Statistical analysis title	Cox regression
Comparison groups	Experimental arm B v Control arm A
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.18

Secondary: 3-year distant metastasis

End point title	3-year distant metastasis
End point description:	The cumulative incidence of locoregional recurrence and distant metastases was defined as the time between randomization and occurrence of any locoregional recurrence (after R0/1 resection of the primary tumor) and distant metastases, respectively, irrespective of whether this was a first event or not.
End point type	Secondary
End point timeframe:	Time from randomization to event listed below

End point values	Control arm A	Experimental arm B	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	156	150	306	
Units: Events	31	25	56	

Statistical analyses

Statistical analysis title	Cox regression
Comparison groups	Experimental arm B v Control arm A
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.43

Secondary: 3-year Overall survival

End point title	3-year Overall survival
End point description:	
Overall survival (OS) was defined as time from randomization to death from any cause.	
End point type	Secondary
End point timeframe:	
Time from randomization to death	

End point values	Control arm A	Experimental arm B	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	156	150	306	
Units: Events	14	15	29	

Statistical analyses

Statistical analysis title	Cox regression
Comparison groups	Experimental arm B v Control arm A

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	2.27

Secondary: Acute Adverse Effects during chemoradiotherapy

End point title	Acute Adverse Effects during chemoradiotherapy
End point description:	
End point type	Secondary
End point timeframe:	
During chemoradiotherapy	

End point values	Control arm A	Experimental arm B	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	151 ^[2]	149 ^[3]	300 ^[4]	
Units: Events				
Grade 1-2	94	107	201	
Grade 3	51	36	87	
Grade 4	4	4	8	
Grade 5	1	1	2	

Notes:

[2] - patients started CRT

[3] - patients started CRT

[4] - patients started CRT

Statistical analyses

No statistical analyses for this end point

Secondary: Acute Adverse Effects during chemotherapy

End point title	Acute Adverse Effects during chemotherapy
End point description:	
End point type	Secondary
End point timeframe:	
during chemotherapy	

End point values	Control arm A	Experimental arm B	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	156	140 ^[5]	296 ^[6]	
Units: Events				
Grade 1-2	117	112	229	
Grade 3	33	25	58	
Grade 4	1	5	6	
Grade 5	0	0	0	

Notes:

[5] - patients who started chemotherapy

[6] - patients who start chemotherapy

Statistical analyses

No statistical analyses for this end point

Secondary: Chronic toxicity after 36 months

End point title	Chronic toxicity after 36 months
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End point description:

End point type	Secondary
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End point timeframe:

Chronic toxicity 36 months after completion of treatment

End point values	Control arm A	Experimental arm B	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	85 ^[7]	66 ^[8]	151	
Units: Events				
Grade 1-2	43	52	95	
Grade 3-4	10	8	18	

Notes:

[7] - available patients

[8] - available patients

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any such occurrence or worsening of a pre-existing medical condition from the time that a subject has received the first dose of study treatment until the End of Treatment Visit or 30 days after the last dose of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B
Reporting group description: -	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 156 (44.23%)	45 / 150 (30.00%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thromboembolic event			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 156 (1.92%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aneurysm			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 156 (1.28%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Visceral arterial ischemia alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 156 (0.00%) 0 / 0 0 / 0	1 / 150 (0.67%) 0 / 1 0 / 0	
General disorders and administration site conditions General physical health deterioration alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	4 / 156 (2.56%) 6 / 6 0 / 0	3 / 150 (2.00%) 3 / 3 0 / 0	
fever alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 156 (1.28%) 1 / 2 0 / 0	1 / 150 (0.67%) 0 / 1 0 / 0	
Influenza alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 156 (0.64%) 1 / 1 0 / 0	0 / 150 (0.00%) 0 / 0 0 / 0	
Extravasation alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 156 (0.64%) 1 / 1 0 / 0	0 / 150 (0.00%) 0 / 0 0 / 0	
Disease progression alternative assessment type: Non-systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 156 (0.64%) 0 / 1 0 / 0	0 / 150 (0.00%) 0 / 0 0 / 0	
Immune system disorders Allergic reaction			

alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 156 (1.28%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Epididymitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
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			
Atelectasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mania			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutropenia	Additional description: Panzytopenia		
subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
creatinine increased			

subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Small intestinal perforation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
car incident			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak	Additional description: Post-OP		
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 156 (6.41%)	9 / 150 (6.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 156 (3.85%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal stoma leak	Additional description: Post-OP		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative hemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 156 (1.28%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Venous injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 156 (0.64%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
stroke			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 156 (1.28%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 156 (1.28%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 156 (1.28%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 156 (5.77%)	4 / 150 (2.67%)	
occurrences causally related to treatment / all	9 / 9	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus	Additional description: Post-OP		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 156 (1.28%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mucositis management	Additional description: Mucositis oral		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 156 (1.28%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal hemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 156 (1.28%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal stenosis	Additional description: Post-OP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction	Additional description: Post-OP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
stomach pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus	Additional description: Post-OP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
esophagitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus perforation	Additional description: Post-OP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Keratosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence	Additional description: Post-OP		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (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			
Abscess soft tissue	Additional description: Post-OP		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (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			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			
alternative assessment type: Non-systematic	Additional description: Post-OP		
subjects affected / exposed	1 / 156 (0.64%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 156 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 156 (0.64%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 156 (100.00%)	149 / 150 (99.33%)	
Investigations			
Leukocytes decreased			
subjects affected / exposed	80 / 156 (51.28%)	94 / 150 (62.67%)	
occurrences (all)	99	132	
Neutrophil count decreased			
subjects affected / exposed	37 / 156 (23.72%)	40 / 150 (26.67%)	
occurrences (all)	44	53	
Platelet count decreased			
subjects affected / exposed	75 / 156 (48.08%)	58 / 150 (38.67%)	
occurrences (all)	85	76	
Dysgeusia			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 156 (7.05%)	4 / 150 (2.67%)	
occurrences (all)	11	4	
Injury, poisoning and procedural complications			
Dermatitis radiation			
subjects affected / exposed	63 / 156 (40.38%)	57 / 150 (38.00%)	
occurrences (all)	71	62	
Anastomotic leak	Additional description: not further specified		
subjects affected / exposed ^[1]	16 / 142 (11.27%)	16 / 142 (11.27%)	
occurrences (all)	16	16	
Urinary retention postoperative			
subjects affected / exposed ^[2]	21 / 142 (14.79%)	14 / 142 (9.86%)	
occurrences (all)	21	14	
Erectile dysfunction			
subjects affected / exposed ^[3]	6 / 96 (6.25%)	5 / 95 (5.26%)	
occurrences (all)	6	5	
Ileus			
subjects affected / exposed ^[4]	8 / 142 (5.63%)	12 / 142 (8.45%)	
occurrences (all)	8	12	
postoperative hemorrhage	Additional description: not further specified		

subjects affected / exposed ^[5] occurrences (all)	4 / 142 (2.82%) 4	5 / 142 (3.52%) 5	
Wound complication sacral subjects affected / exposed ^[6] occurrences (all)	15 / 142 (10.56%) 15	16 / 142 (11.27%) 16	
Wound complication abdominal subjects affected / exposed ^[7] occurrences (all)	16 / 142 (11.27%) 16	8 / 142 (5.63%) 8	
Postoperative pain alternative assessment type: Non-systematic subjects affected / exposed ^[8] occurrences (all)	9 / 142 (6.34%) 9	9 / 142 (6.34%) 9	
Polyneuropathy alternative assessment type: Non-systematic subjects affected / exposed ^[9] occurrences (all)	7 / 142 (4.93%) 7	7 / 142 (4.93%) 7	
Nervous system disorders Paresthesia subjects affected / exposed occurrences (all)	68 / 156 (43.59%) 82	67 / 150 (44.67%) 80	
Oxaliplatin-induced paresthesia subjects affected / exposed occurrences (all)	Additional description: Wassermann Score		
	113 / 156 (72.44%) 126	103 / 150 (68.67%) 132	
Dizziness alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	8 / 156 (5.13%) 8	11 / 150 (7.33%) 11	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	102 / 156 (65.38%) 136	99 / 150 (66.00%) 148	
Fever subjects affected / exposed occurrences (all)	19 / 156 (12.18%) 24	11 / 150 (7.33%) 11	
Pain	Additional description: not further specified		

subjects affected / exposed occurrences (all)	89 / 156 (57.05%) 113	75 / 150 (50.00%) 93	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	105 / 156 (67.31%) 137	98 / 150 (65.33%) 135	
Immune system disorders Allergic reaction to excipient subjects affected / exposed occurrences (all)	10 / 156 (6.41%) 11	10 / 150 (6.67%) 13	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	129 / 156 (82.69%) 163	101 / 150 (67.33%) 120	
Vomiting subjects affected / exposed occurrences (all)	34 / 156 (21.79%) 40	28 / 150 (18.67%) 31	
Mucositis oral subjects affected / exposed occurrences (all)	51 / 156 (32.69%) 64	33 / 150 (22.00%) 38	
Constipation subjects affected / exposed occurrences (all)	44 / 156 (28.21%) 57	37 / 150 (24.67%) 43	
Proctitis subjects affected / exposed occurrences (all)	66 / 156 (42.31%) 73	65 / 150 (43.33%) 78	
Nausea subjects affected / exposed occurrences (all)	98 / 156 (62.82%) 137	86 / 150 (57.33%) 113	
Anorexia	Additional description: Loss of appetite		
alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	9 / 156 (5.77%) 9	4 / 150 (2.67%) 4	
Rectal haemorrhage alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 11	6 / 150 (4.00%) 6	
Respiratory, thoracic and mediastinal disorders Dyspnea subjects affected / exposed occurrences (all)	24 / 156 (15.38%) 29	17 / 150 (11.33%) 23	
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysesthesia syndrome alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	6 / 156 (3.85%) 6	1 / 150 (0.67%) 1	
Renal and urinary disorders Cystitis noninfective subjects affected / exposed occurrences (all) Urinary urgency subjects affected / exposed occurrences (all) Acute kidney injury subjects affected / exposed occurrences (all)	33 / 156 (21.15%) 38 42 / 156 (26.92%) 46 31 / 156 (19.87%) 34	33 / 150 (22.00%) 42 36 / 150 (24.00%) 44 16 / 150 (10.67%) 18	
Infections and infestations Infection	Additional description: not specified		
subjects affected / exposed occurrences (all)	20 / 156 (12.82%) 24	19 / 150 (12.67%) 21	

Notes:

[1] - 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: The total number exposed includes only patients who underwent surgery (284).

[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: The total number exposed includes only patients who underwent surgery (284).

[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: The total number exposed includes only patients who underwent surgery (284).

[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: The total number exposed includes only patients who underwent surgery (284).

[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: The total number exposed includes only patients who underwent surgery (284).

[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: The total number exposed includes only patients who underwent surgery (284).

[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: The total number exposed includes only patients who underwent surgery (284).

[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: The total number exposed includes only patients who underwent surgery (284).

[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: The total number exposed includes only patients who underwent surgery (284).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2016	Amendment 1: Extension if recruitment period, Staff changes
11 July 2019	Amendment 2: Change of the CRO

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Our trial has limitations. First, there was no central pathology evaluation. Second, because pCR constituted the primary end point of the study, long-term clinical outcome was not evaluated but will be reported in the future when mature follow-up data are available.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31150315>

<http://www.ncbi.nlm.nih.gov/pubmed/34792531>