Clinical trial results:
Translational Validation Trial-B, an add-on phase I/II study to the Clinical Research Unit (Klinische Forschergruppe) KFO179-2

Summary

EudraCT number	2011-004228-37
Trial protocol	DE
Global end of trial date	31 March 2021

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	TransValid-KFO179/GRCSG-B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1132-0235

Notes:

Sponsors

Sponsor organisation name	Universitätsmedizin Göttingen (UMG), Georg-August-Universität Göttingen Stiftung Öffentlichen Rechts
Sponsor organisation address	Robert-Koch-Straße 40, Göttingen, Germany, 37075
Public contact	Studienzentrum UMG, Universitätsmedizin Göttingen (UMG), +49 5513960812, sz-umg.sponsor-qm@med.uni-goettingen.de
Scientific contact	Prof. Dr. Torsten Liersch , Klinik für Allgemein- Viszeral- und Kinderchirurgie, Universitätsmedizin Göttingen (UMG), +49 5513963876, studiensek-chirurgie@med.uni-goettingen.de

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	12 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2021
Global end of trial reached?	Yes
Global end of trial date	31 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to establish the feasibility and to receive first data on the efficacy of an innovative sequential combination of established pre-operative intensified RCT (5-FU+Oxaliplatin) with consecutively intensive but shortened preoperative FOLFOXchemotherapy (5-FU+Oxaliplatin) followed by TME-surgery.
Primary Objectives:
- The primary objectives for this evaluation will be toxicity and histopathologically confirmed complete tumor remission (pCR).
- The data will be compared exploratively to the separate TransValid-KFO179/GRCSG-Trial-A (validation study, n=200 patients) and to expectations derived from historical data (e.g. the large CAO/AIO/ARO-94 as well as -04 trial of the German Rectal Cancer Study Group [GRCSG] and others).

Protection of trial subjects:

All participants underwent an exon-14-skipping-test to preclude a genetic dihydropyrimidine dehydrogenase dysfunction (DPYD*2A). This measure was intended to avoid unexpected, more severe toxicities as a result of impaired DPD enzyme function with consecutive, uncontrolled 5-FU dose escalation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	28
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were planned to enter the study at three study sites. Total recruitment was performed by only two sites, University Medical Center Göttingen and University Medical Center of Frankfurt / Main. The third site has to be deregistered caused by inactivity. The recruitment period extended from April 12, 2013 to June 30, 2017.

Pre-assignment

Screening details:

A total of 55 participants with locally advanced rectal cancer was screened for eligibility, of whom 50 patients entered the study. Five patients had to be excluded due to the inclusion/exclusion criteria of the TransValid-B study.

Period 1

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

Blinding implementation details:

As there was only one treatment regimen, the intervention was not blinded.

Arms

Arm title	Overall Trial

Arm description:

CRT: 5-FU: 250 mg/m2 civ, d1-d14 + d22-d35; OX: 50 mg/m2 2h iv d1, d8, d22 + d35.
3 applications of FOLFOX: FA: 400 mg/m2 2h iv, d1; OX: 100 mg/m2 2h iv, d1; 5-FU 2.400 mg/m2 46h civ, on d1 + d2

Arm type	Investigation of a new treatment regimen
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intraportal use

Dosage and administration details:

CRT: 5-FU: 250 mg/m2 civ, d1-d14 + d22-d35
kCTx: 5-FU: 2.400 mg/m2 46h civ, on d1 + d2

Investigational medicinal product name	Folinacid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intraportal use

Dosage and administration details:

kCTx: FA: 400 mg/m2 2h iv, d1

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intraportal use

Dosage and administration details:

CRT: OX: 50 mg/m2 2h iv d1, d8, d22 + d35
kCTx: OX: 100 mg/m2 2h iv, d1

Number of subjects in period 1	Overall Trial
Started	48
Staging I	48
CRT	48
Staging II	48
FOLFOX-CTx	46
Staging III	46
TME-surgery	44
Staging IV	44
Follow-up	43
Completed	43
Not completed	5
Adverse event, serious fatal	2
Progression of disease	1
Refusal of surgery ("watch and wait")	2

Baseline characteristics

Reporting groups	
Reporting group title	overall trial
Reporting group description:	
Intention-to-treat-population (ITT)	

Reporting group values	overall trial	Total	
Number of subjects	48	48	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	19	19	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	60.77		
standard deviation	± 9.41	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	38	38	
ECOG-Status Units: Subjects			
ECOG-0	40	40	
ECOG-1	8	8	
BMI (grouped) Units: Subjects			
underweight	2	2	
normal weigth	20	20	
overweight	16	16	
obese	8	8	
missing	2	2	
Grading Units: Subjects			
G1	1	1	
G2	44	44	
G3	3	3	
Tumor location			
Classification: low (< 6 cm); mid (6-11 cm)			
Units: Subjects			

lower rectum	16	16	
mid rectum	32	32	
Clinical (c) UICC-stages			
rES, MRI and CT findings were summarized.			
Units: Subjects			
cUICC-III	42	42	
cUICC-IV	6	6	
Body height (cm)			
Units: cm			
arithmetic mean	174.30		
standard deviation	± 7.29	-	
Body weigth (kg)			
Units: kg			
arithmetic mean	78.64		
standard deviation	± 13.16	-	
Body-Mass-Index			
Units: kg/m2			
arithmetic mean	25.77		
standard deviation	± 4.31	-	
Tumormarker - CEA			
Units: ng/ml			
arithmetic mean	8.88		
standard deviation	± 12.93	-	
Tumormarker - CA 19-9			
Units: U/ml			
arithmetic mean	26.97		
standard deviation	± 55.86	-	
Tumor location			
Distance between the anal verge (av) and the inferior tumor margin.			
Units: cm			
arithmetic mean	6.73		
standard deviation	± 3.08	-	

End points

End points reporting groups

Reporting group title	Overall Trial

Reporting group description:

CRT: 5-FU: 250 mg/m2 civ, d1-d14 + d22-d35; OX: 50 mg/m2 2h iv d1, d8, d22 + d35.
3 applications of FOLFOX: FA: 400 mg/m2 2h iv, d1; OX: 100 mg/m2 2h iv, d1; 5-FU 2.400 mg/m2 46h civ, on d1 + d2

Primary: Acute toxicity

End point title	Acute toxicity[1]

End point description:

Acute toxicity grading (according to NCI-CTC-AE, Vs. 4.0) included the proportion of patients with at least one toxicity event.

End point type	Primary

End point timeframe:

Acute toxicity assessment during TNT and 4 weeks postoperatively.

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: Acute toxicity (grading according to National Cancer Institute Common Terminology Criteria for Adverse Events, NCI-CTC-AE, Vs 4.03) and the proportion of patients with atleast one CTC event < 4 weeks after TNT.
We hypothesized that TNT-associated toxicity, esp. AEs grade ≥ 3, will not reach 35%as shown in the adjuvant setting of the CAO/ARO/AIO-04 trial (Hofheinz et al. 2018).

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: 0-5				
grade 1	341			
grade 2	119			
grade 3	52			
grade 4	2			
grade 5	1			

Statistical analyses

No statistical analyses for this end point

Primary: Complete tumor remission

End point title	Complete tumor remission[2]

End point description:

The histopathological confirmed complete LARC remission (CR) was defined as ypT0 and ypN0 status or as ypUICC stage 0. Near CR (nCR) was defined as ypT1/T2 and ypN0 or ypUICC stage I.
Comparison with the clinically determined CR/nCR (defined as no endoluminal visible and/or palpable cancer formation without any radiological findings or rES signs for residual cancer after TNT) for assessment of the accuracy.

End point type	Primary

End point timeframe:

After TNT and TME within the histopathological analyses.

Notes:

[2] - 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: We hypothesized that TNT could enhance the CR rate up to 20%, whereas this CR rate was approximately achieved in 8% - 15% after MMT in the CAO/ARO/AIO-94 and -04 trials (Sauer et al. 2004, 2012; Rödel et al. 2012, 2015).

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: 0-1				
CR	7			
nCR	10			
not	31			

Statistical analyses

No statistical analyses for this end point

Primary: Recurrence-free-survival (RFS)

End point title	Recurrence-free-survival (RFS)[3]

End point description:

Time from surgery to detection of an event (LR, FM or death from any cause; second cancers were ignored; loss of contact was censored). Showing the survival in patients with UICC stages ≤ II, II and ≥ III after TNT. The Kaplan Meier estimated survival curves are shown in a chart. The 3-y and 5-y RFS rates were 73.9% (95%-CI: 61.8%; 88.5%) and 71.0% (95%-CI: 58.3%; 86.4%).

End point type	Primary

End point timeframe:

Recurrence-free-survival (RFS) estimation after 36 and 60 months after TME-surgery as determined during follow-up.

Notes:

[3] - 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 clinical aim of this proof-of-concept study was to achieve higher rates of recurrence-free survival (RFS, > 75% at 3-y / > 70% at 5-y) compared to the recently published trials CAO/ARO/AIO-94-, -04-, -12- and PETACC-6 (Sauer et al. 2004, 2012; Rödel et al. 2010, 2012, 2015; Fokas et al. 2019, 2022; Schmoll et al. 2013, 2021). The endpoints, methods and analyses of the Trans-Valid-B-trial had been given in the statistical analysis plan (SAP Vs 1.2/ 2022-03-24).

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Patients at risk				
day: 0	43			
day: 1000	30			
day: 2000	6			
day: 3000	0			

Attachments (see zip file)	RFS (R0, 60 months follow-up) after TME-surgery /TVB_RFS.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of local recurrence

End point title	Cumulative incidence of local recurrence

End point description:

Local-recurrence (LR) estimation measured as a cumulative incidence. The LR is defined as locoregional failure within 5 cm of the anastomotic region (after LAR) or in the pelvic or perineal area (after APR).

End point type	Secondary

End point timeframe:

Timeperiod from surgery to detection of a local recurrence.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Number of local recurrences	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of distant metastases

End point title	Cumulative incidence of distant metastases

End point description:

Distant metastases (DM) estimation measured as a cumulative incidence. The DM is defined as radiological / pathological event of the same cancer.

End point type	Secondary

End point timeframe:

Timeperiod from surgery to detection of a distant metastases.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Number of distant metastases	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Circumferential resection margin (CRM)

End point title	Circumferential resection margin (CRM)

End point description:

Proportion of patients with circumferential resection margin (CRM: < 1 mm vs ≥ 1 mm; CRM: < 2 mm vs ≥ 2 mm (according to Nagtegaal et al. 2005, Wittekind et al. 2009).

End point type	Secondary

End point timeframe:

After TNT, within histopathological examinations.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: 0-2				
<1 mm	2			
≥ 1 mm	38			
< 2 mm	4			
≥ 2 mm	36			

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor regression grading (TRG)

End point title	Tumor regression grading (TRG)

End point description:

Proportion of patients with tumor regression grades (TRG 0 to 4, Dworak et al. 1997).

End point type	Secondary

End point timeframe:

After TNT, within histopathological examinations.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: 0;1;2;3;4				
TRG 0	1			
TRG 1	5			
TRG 2	19			
TRG 3	11			
TRG 4	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Residual lymph node status

End point title	Residual lymph node status

End point description:

Proportion of patients with nodal status (ypN0 to ypN2) and subgroups (ypN1 a-c, ypN2 a-b); number of lymph nodes (LN) and lymph node metastases (LNM) in total and per specimen; the quotient (ratio) of total LNM/LN and of LNM/LN per specimen.

End point type	Secondary

End point timeframe:

After TNT, within histopathological examinations.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: 0;1				
ypN0	31			
ypN1a	6			
ypN1b	3			
ypN2x	1			
ypN2a	1			
ypN2b	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative 30 d and 60 d mortality

End point title	Postoperative 30 d and 60 d mortality

End point description:

The 30d mortality rate was 2.3% and and consequently the 30 d and 60 d postsurgical survival rates amounted 97.7%.

End point type	Secondary

End point timeframe:

After TNT, within 30 and 60 days.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: 0;1	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Postsurgical morbidity

End point title	Postsurgical morbidity

End point description:

Postsurgical complications within 4 weeks after TME-surgery (e.g. anastomotic leaks, wound healing disorders).
Late complications > 4 weeks after qTME (diarrhea, defacation problems, late anastomotic leaks or stenoses, loss of sphincter function, need for a diverting stoma, low anterior resection syndrome (LARS)).
Events will categorized according to the NCI-CTC-AE Vs. 4.0 and/or Dindo-Clavien-classification.

Correlation of the acute peri-/postsurgical complications with the patients` ASA-score.

End point type	Secondary

End point timeframe:

Postoperatively

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: grade 1 - 5				
peri-/postop. CTCAE ≥ 2	31			
peri-/postop. CTCAE ≥ 3	15			
late CTCAE ≥ 2	104			
late CTCAE ≥ 3	49			

Attachments (see zip file)	Peri-/postoperative CTC-AEs associated to TME- Patients with late CTC-AEs during follow-up (1-5) Correlation between ASA score and postsurgical

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of TME surgery

End point title	Quality of TME surgery

End point description:

Peri- and postoperative assessment of TME according to MERCURY-criteria (Quirke et al. 2009).

End point type	Secondary

End point timeframe:

Peri- and postoperatively, assessed by surgeon and histopathologist.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: poor, moderate, optimal				
poor - periop.	0			
moderate - periop.	4			
optimal - periop.	36			
missing - periop.	4			
poor - postop.	1			
moderate - postop.	3			
optimal - postop.	40			
missing - postop.	0			

Attachments (see zip file)	Quality of TME-surgery and interrater reliability

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free survival (DFS)

End point title	Disease-free survival (DFS)

End point description:

Time from surgery to detection of an event (LR, FM, second cancer or death from any cause; loss of contact was censored).

End point type	Secondary

End point timeframe:

Disease-free survival (DFS) estimation after 36 and 60 months after TME-surgery as determined during follow-up.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Patients at risk				
day: 0	43			
day: 1000	30			
day: 2000	5			
day: 3000	0			

Attachments (see zip file)	DFS (R0, 60 months follow-up) after qTME /TVB_DFS.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Cancer-specific survival (CSS)

End point title	Cancer-specific survival (CSS)

End point description:

Time from surgery to detection of an event (death from cancer; LR, FM, second cancers, death from any cause than cancer were ignored; loss of contact was censored).
Including competing risk to non-cancer specific death.

Cancer-specific survival (CSS) and competing risk to non-cancer specific death during 60 months follow-up. CSS was defined as the time interval between study entry and the date of death caused by the same cancer and/or progression. Patients who died by any other cause had been regarded as competing risks. During follow-up 1 patient suffered an urothel-carcinoma (pat_5535) 20 months after qTME of the LARC. Later, LM of this secondary cancer occurred and led to death. Another patient (pat_5603) died 5 days after qTME due to heart failure and massive cerebral bleeding.

The plot shows the estimates of the non-parametric Aalen-Johansen estimate of the cumulative incidence functions (competing risks data); other: pat_5603 with death not due to cancer or toxicity

End point type	Secondary

End point timeframe:

Cancer-specific survival (CSS) estimation after 36 and 60 months after TME-surgery as determined during follow-up.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Patients at risk				
detection of an event	2			

Attachments (see zip file)	Cancer-specific survival (CSS) with competing risk/TVB_CSS.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Sphincter-sparing surgery

End point title	Sphincter-sparing surgery

End point description:

Rate of spincter-sparing surgery: among patients for whom sphincter preservation was deemed feasible at baseline; in patients who were able to preserve the sphincter muscle after completion of TNT; Accuracy of staging (III) and repeated judgement about feasibility of sphincter preservation as a result of TNT induced longitudinal tumor shrinkage and / or infiltration depth (ypT-status).

End point type	Secondary

End point timeframe:

Pre- and postoperative assessment of sphincter preservation

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	44[4]			
Units: 0-1				
baseline ssTME - yes	37			
baseline ssTME - no	7			
actual ssTME - yes	32			
actual ssTME - no	10			

Notes:

[4] - PP patients` cohort

Attachments (see zip file)	Sphincter-saving TME-surgery/TVB_spinctersparing_surgery.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of ypUICC-stages

End point title	Proportion of ypUICC-stages

End point description:

Comparison of ypUICC-stages 0-IV (including subgroups II a-c, III a-c, IV a-b); Number of patients with confirmed ypUICC <= I + <= II.

End point type	Secondary

End point timeframe:

Postoperative examination of the histopathological parameters.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: 1;0				
ypUICC-0	6			
ypUICC-I	9			

ypUICC-II	14			
ypUICC-III	10			
ypUICC-IV	5			
ypUICC ≤ I	15			
ypUICC ≥ III	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance to TNT

End point title	Compliance to TNT

End point description:

Patient`s compliance to TNT was measured as the number of patients willing to complete the treatment sequence CRT CTx TME-surgery.

End point type	Secondary

End point timeframe:

Examination postoperative.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: 1;0				
TNT complete	45			

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to preoperative treatment

End point title	Adherence to preoperative treatment

End point description:

The adherence to the treatment sequence CRT CTx was measured as number of completely applied irradiation and CTx per patient.

End point type	Secondary

End point timeframe:

Examination after TNT.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: 1;0				
Adherence number	42			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Time from surgery to detection of an event (death from any cause; LR, FM, second cancers were ignored; loss of contact was censored).

End point type	Secondary

End point timeframe:

Overall survival (OS) estimation after 36 and 60 months after TME-surgery as determined during follow-up.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Patients at risk				
day: 0	48			
day: 1000	43			
day: 2000	11			
day: 3000	0			

Attachments (see zip file)	Overall survival (OS) /TVB_OS.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-treatment-failure (TTF)

End point title	Time-to-treatment-failure (TTF)

End point description:

Time-to-treatment-failure (TTF) was defined as the interval between study entry and any signs of progressive disease (PD) for patients in UICC stage IV or of any local regrowth in patients with refusal of TME or in patients after TNT with any local or metastatic event related to rectal cancer.

End point type	Secondary

End point timeframe:
Measured from study entry.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Patients at risk				
day: 0	48			
day: 1000	36			
day: 2000	8			
day: 3000	0			

Attachments (see zip file)	Time-to-treatment failure (TTF) and survival/TVB_TTF.tif

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events have been monitored during 2 cycles of CRT, 3 applications of FOLFOX-CTx, in between CRT and CTx and during follow-up.

Adverse event reporting additional description:

Acute and late toxicity of the preoperative CRT and preoperative FOLFOX-CTx were classified according to the NCI-CTC-AE (vs 4.0).

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTC-AE
Dictionary version	4.0

Reporting groups

Reporting group title	Overall Trial

Reporting group description:

Included 48 participants.

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 48 (31.25%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Deterioration general health status / tumor perforation	Additional description: Event occurred during CRT; SUSAR. Outcome fatal. During the first period of CRT a patient (pat_5505, f, 53-y, cUICC III) died due to septic shock and tumor-toxic cardiovascular failure. ((y)pUICC-II or (y)pT4b N0 (0/43 LN) L/V/Pn0 G2, TRG 2).		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiovascular arrest	Additional description: Event occurred postoperatively. Outcome fatal.		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Portdysfunction	Additional description: Event occurred between CRT and CTx; resolved with sequelae. Patient received portimplantation.		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Port needle dislocation	Additional description: Event occurred during CRT; resolved without sequelae.		

subjects affected / exposed	3 / 48 (6.25%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Soft-tissue infection (area of the port)	Additional description: Event occurred during CRT; resolved without sequelae.		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Deterioration of persistent anastomotic leakage	Additional description: Event occurred postoperatively; resolved with sequelae. Event ended with additional surgical intervention (Hartmann-Situation).		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus	Additional description: Patient 1: Event occurred between informed consent and start of therapy. Resolved without sequelae. Patient 2: Event occurred during CRT; resolved without sequelae. Patient was withdrawn due to peritoneal-carcinosis (drop-out).		
subjects affected / exposed	2 / 48 (4.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea	Additional description: Event occurred during CTx; resolved without sequelae.		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus	Additional description: Event occurred postoperatively; resolved without sequelae.		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Coprostasis	Additional description: Event occurred postoperatively; resolved without sequelae.		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anastomotic leakage	Additional description: Event occurred postoperatively; ongoing, no therapy. Patient refuses recommended surgical intervention.		

subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Sacral wound healing disorder	Additional description: Event occurred postoperatively; ongoing, no therapy. Patient refuses recommended surgical intervention.		
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 48 (100.00%)		
Investigations			
Creatinine increased	Additional description: Acute adverse event occured during TNT; 9x grade 1, 1x grade 2; ≥ grade 2: 1x		
subjects affected / exposed	10 / 48 (20.83%)		
occurrences (all)	10		
White blood cell count decreased	Additional description: Acute adverse event occured during TNT; 17x grade 1, 11x grade 2, 4x grade 3; ≥ grade 2: 15x, ≥ grade 3: 4x		
subjects affected / exposed	32 / 48 (66.67%)		
occurrences (all)	32		
Neutrophil count decreased	Additional description: Acute adverse event occured during TNT; 3x grade 1, 3x grade 2, 1x grade 3; ≥ grade 2: 4x, ≥ grade 3: 1x		
subjects affected / exposed	7 / 48 (14.58%)		
occurrences (all)	7		
Platelet count decreased	Additional description: Acute adverse event occured during TNT; 25x grade 1, 1x grade 2; ≥ grade 2: 1x		
subjects affected / exposed	26 / 48 (54.17%)		
occurrences (all)	26		
Injury, poisoning and procedural complications			
RT-related dermatitis	Additional description: Acute adverse event occured during TNT; 17x grade 1, 8x grade 2, 2x grade 3; ≥ grade 2: 19x, ≥ grade 3: 2x		
subjects affected / exposed	27 / 48 (56.25%)		
occurrences (all)	27		
Nervous system disorders			
Erectile dysfunction	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 3x grade 1, 10x grade 2, 3x grade 3; ≥ grade 2: 13x, ≥ grade 3: 3x		

subjects affected / exposed	16 / 48 (33.33%)		
occurrences (all)	16		
Oxaliplatin induced neurotoxicity (chronic)	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 2x grade 2, 1x grade 2, 24x grade 3; ≥ grade 2: 25x, ≥ grade 3: 24x		
alternative dictionary used: Wassermann-Score 1			
subjects affected / exposed	27 / 48 (56.25%)		
occurrences (all)	27		
Peripheral sensory neuropathy (chronic)	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 14x grade 1, 13x grade 2, 2x grade 3; ≥ grade 2: 15x, ≥ grade 3: 2x		
subjects affected / exposed	29 / 48 (60.42%)		
occurrences (all)	29		
Oxaliplatin induced neurotoxicity (acute)	Additional description: Acute adverse event occured during TNT; 18 grade 1, 5x grade 2, 17x grade 3; ≥ grade 2: 22x, ≥ grade 3: 17x		
alternative dictionary used: Wassermann-Score 1			
subjects affected / exposed	30 / 48 (62.50%)		
occurrences (all)	30		
Peripheral sensory neuropathy (acute)	Additional description: Acute adverse event occured during TNT; 28x grade 1, 11x grade 2; ≥ grade 2: 11x		
subjects affected / exposed	39 / 48 (81.25%)		
occurrences (all)	39		
General disorders and administration site conditions			
Fatigue	Additional description: Acute adverse event occured during TNT; 30x grade 1, 1x grade 2		
subjects affected / exposed	31 / 48 (64.58%)		
occurrences (all)	31		
Fever	Additional description: Acute adverse event occured during TNT; 3x grade 1, 1 grade 2; ≥ grade 2: 1x		
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Pain	Additional description: Acute adverse event occured during TNT; 13x grade 1, 15x grade 2		
subjects affected / exposed	28 / 48 (58.33%)		
occurrences (all)	28		
Other AEs postoperative (free text)	Additional description: postoperative; 6x grade 2, 3x grade 3, 1x grade 5; ≥ grade 2: 10x, ≥ grade 3: 4x		
subjects affected / exposed	10 / 48 (20.83%)		
occurrences (all)	10		
Other AEs acute (free text)	Additional description: Acute adverse event occured during TNT: 4x grade 1, 6x grade 2, 5x grade 3, 1x grade 4; ≥ grade 2: 12x, ≥ grade 3: 6x		
subjects affected / exposed	16 / 48 (33.33%)		
occurrences (all)	16		

Other AEs chronic (free text)	Additional description: Chronic toxicity (> 4 weeks postop during follow-up): 6x grade 1, 8x grade 2, 9x grade 3; ≥ grade 2: 17x, ≥ grade 3: 9x		
subjects affected / exposed	23 / 48 (47.92%)		
occurrences (all)	23		
Blood and lymphatic system disorders			
Anaemia	Additional description: Acute adverse event occured during TNT; 39x grade 1, 4x grade 2; ≥ grade 2: 4x		
subjects affected / exposed	43 / 48 (89.58%)		
occurrences (all)	43		
Immune system disorders			
Allergic reaction	Additional description: Acute adverse event occured during TNT; 3x grade 1		
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Gastrointestinal disorders			
Anastomotic leak	Additional description: Postoperative; 1x grade 2, 5x grade 3; ≥ grade 2: 6x, ≥ grade 3: 5x		
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	6		
Ileus	Additional description: Postoperative; 3x grade 2; 1x grade 4; ≥ grade 2: 4x, ≥ grade 3: 1x		
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Anastomotic stenosis	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 3x grade 1, 1x grade 2, 2x grade 3; ≥ grade 2: 3x, ≥ grade 3: 2x		
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	6		
Diarrhoea (chronic)	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 8x grade 1, 9x grade 2, 7x grade 3; ≥ grade 2: 16x, ≥ grade 3: 7x		
subjects affected / exposed	24 / 48 (50.00%)		
occurrences (all)	24		
Proctitis (chronic)	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 6x grade 1		
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	6		
Faecal incontinence	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 10x grade 1, 6x grade 2, 1x grade 3; ≥ grade 2: 7x, ≥ grade 3: 1x		
subjects affected / exposed	17 / 48 (35.42%)		
occurrences (all)	17		
Diarrhoea (acute)	Additional description: Acute adverse event occured during TNT; 12x grade 1, 8x grade 2, 3x grade 3; ≥ grade 2: 11x, ≥ grade 3: 3x		
subjects affected / exposed	23 / 48 (47.92%)		
occurrences (all)	23		
Vomiting	Additional description: Acute adverse event occured during TNT; 8x grade 1		

subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	8		
Mucositis oral	Additional description: Acute adverse event occured during TNT; 11x grade 1, 2x grade 2; ≥ grade 2: 2x		
subjects affected / exposed	13 / 48 (27.08%)		
occurrences (all)	13		
Constipation	Additional description: Acute adverse event occured during TNT; 7x grade 1, 1x grade 2; ≥ grade 2: 1x		
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	8		
Proctitis (acute)	Additional description: Acute adverse event occured during TNT; 21x grade 1, 13x grade 2, 4x grade 3; ≥ grade 2: 17x, ≥ grade 3: 4x		
subjects affected / exposed	38 / 48 (79.17%)		
occurrences (all)	38		
Nausea	Additional description: Acute adverse event occured during TNT; 20x grade 1, 3x grade 2; ≥ grade 2: 3x		
subjects affected / exposed	23 / 48 (47.92%)		
occurrences (all)	23		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Acute adverse event occured during TNT; 2x grade 1, 1x grade 2, 1x grade 3, 1x grade 4; ≥ grade 2: 3x, ≥ grade 3: 2x		
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Wound healing disorder abdominal	Additional description: Postoperative; 3x grade 3		
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Wound healing disorder sacral	Additional description: Postoperative; 4x grade 1; 1x grade 2; 1x grade 3; ≥ grade 2: 2x, ≥ grade 3: 1x		
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	6		
Dermatitis radiation	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 3x grade 1		
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Renal and urinary disorders			
Bladder voiding disorder (postoperative)	Additional description: Postoperative; 1x grade 1; 5x grade 2; 4x grade 3; ≥ grade 2: 9x, ≥ grade 3: 4x		
subjects affected / exposed	10 / 48 (20.83%)		
occurrences (all)	10		
Bladder voiding disorder (chronic)	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 8x grade 1, 6x grade 2, 1x grade 3; ≥ grade 2: 7x, ≥ grade 3: 1x		

subjects affected / exposed	15 / 48 (31.25%)		
occurrences (all)	15		
Cystitis (non-infectious) (chronic)	Additional description: Chronic toxicity (> 4 weeks postop during follow-up); 3x grade 1, 1x grade 2; ≥ grade 2: 1x		
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Cystitis (non-infectious) (acute)	Additional description: Acute adverse event occured during TNT; 15x grade 1, 3x grade 2; ≥ grade 2: 3x		
subjects affected / exposed	18 / 48 (37.50%)		
occurrences (all)	18		
Urinary frequency	Additional description: Acute adverse event occured during TNT; 25x grade 1, 3x grade 2; ≥ grade 2: 3x		
subjects affected / exposed	28 / 48 (58.33%)		
occurrences (all)	28		
Infections and infestations			
Infection	Additional description: Acute adverse event occured during TNT; 3x grade 1, 2x grade 2, 1x grade 3; ≥ grade 2: 3x, ≥ grade 3: 1x		
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2014	Amendment by Ethiccomission; Patients Informed Consent Vs 1.4
25 April 2016	Amendment by Ethiccomission; temporary change of the PI (LKP).
12 July 2016	Amendment by BfArM; temporary change of the PI, Protocol Version 1.3
21 July 2016	Amendment by Ethiccomission; Document customization
25 June 2019	Amendment by Ethiccomission; change of the interim PI and return of the former PI (TL); change of the CRO, Protocol Vs 1.4
12 July 2019	Amendment by BfArM; change of the interim PI and return of the former PI (TL); change of the CRO, Protocol Vs 1.4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported