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

Study Protocol

Study Sponsor:	Dean of Medical Faculty, Goethe-University Frankfurt
Coordinating Group:	German Rectal Cancer Study Group Intergroup CAO/ARO/AIO
Study Chairman (LKP):	Prof. Dr. Claus Rödel Dept. of Radiation Therapy and Oncology University Hospital Frankfurt/M. Theodor-Stern-Kai 7 60590 Frankfurt am Main Tel. : 069/6301-5130 Fax : 069/6301-5091 Email: claus.roedel@kgu.de
Study coordinator:	Prof. Dr. Torsten Liersch (CAO, Surgical Oncology) Prof. Dr. Rainer Fietkau (ARO, Radiation Oncology) Prof. Dr. Ralf Hofheinz (AIO, Medical Oncology)
Steering committee:	D. Arnold, H. Becker, R. Fietkau, E. Fokas, T. Friede, U. Graeven, A. Hartmann, A. Hinke, R. Hofheinz, W. Hohenberger, T. Liersch, R. Raab, C. Rödel, R. Sauer, H. Wolff
Data monitoring:	**WiSP GmbH, Langenfeld**
Biostatistics:	Prof. Dr. Tim Friede, Dept. of Medical Statistics University Hospital Göttingen
EudraCT No.:	2011-006310-13
Study Group Code:	CAO/ARO/AIO-12
Protocol version:	v 1.0 final, 16.09.2014

STAFFS AND INSTITUTIONS WITH CENTRAL RESPONSIBILITY:

Study Sponsor:	Dean of Medical Faculty, Goethe-University Frankfurt
Study Chairman (LKP):	Prof. Dr. C. Rödel Dept. of Radiation Therapy and Oncology University Hospital Frankfurt/M. Theodor-Stern-Kai 7 60590 Frankfurt am Main Tel.: 069/6301-5130 Fax: 069/6301-5091 Email: claus.roedel@kgu.de
Study coordinator/ Quality Reference Center	Surgical Oncology: Prof. Dr. T. Liersch Dept. of General. Visceral and Child Surgery University Hospital Göttingen Robert-Koch-Str. 40 37075 Göttingen Tel.: 0551/39-8766 Fax: 0551/39-8758 Email: tliersch@gwdg.de Radiation Oncology: Prof. Dr. Rainer Fietkau Dept. of Radiation Oncology University Hospital Erlangen Universitätsstraße 27 91054 Erlangen Tel.: 09131/85-33405 Fax: 09131/85-39335 Email: rainer.fietkau@uk-erlangen.de PD Dr. Hendrik Wolff Dept. of Radiation Oncology University Hospital Götttingen Robert-Koch-Str. 40 37075 Göttingen Tel.: 0551/39-8866 Fax: 0551/39-8840 Email: hendrik.wolff@med.uni-goettingen.de Medical Oncology: Prof. Dr. Ralf-Dieter Hofheinz Medical Oncology University Medical Center Mannheim Theodor-Kutzer-Ufer 1-3

	68167 Mannheim, Germany Tel.: 0621/383-2855 Fax: 0621/383-2488 Email: ralf.hofheinz@umm.de Pathology Prof. Dr. med. Philipp Ströbel Dept. of Pathology University Hospital Göttingen Robert-Koch-Straße 40 37075 Göttingen Email: philipp.stroebel@med.uni-goettingen.de On behalf of the Pathology Consortium of the GRCSG: Prof. Dr. C. Wittekind, Leipzig, Prof. Dr. Josef Rüschoff, Kassel, Prof. Dr. A. Hartmann, Erlangen Radiology Prof. Dr. U. Attenberger Institute of Clinical Radiology and Nuclear Medicine University Medical Center Mannheim Theodor-Kutzer-Ufer 1-3 68167 Mannheim Tel.: 0621/383-2067 Fax: 0621/383-1910 Email: Ulrike.Attenberger@umm.de
Biostatistics:	Prof. Dr. Tim Friede Prof. Dr. Tim Beissbarth Dept. of Medical Statistics University Hospital Göttingen Humboldtallee 32 37073 Göttingen Tel.: 0551/39-4990 Fax: 0551/39-4995 Email: tim.friede@med.uni-goettingen.de
Data Safety Monitoring Board	N. N.
Monitoring and Data Management:	WiSP GmbH, Langenfeld Dr. Axel Hinke, Heiko Sülberg Tel.: 02173/85313-0 Fax: 02173/85313-11 Email: info@wisp.de
Study Office	Marga Lang-Welzenbach, M.A. Office for Clinical Studies Dept. of Radiation Oncology University Hospital Erlangen

	Universitätsstr. 27 91054 Erlangen Tel.: 09131/85-33968 Fax: 09131/85-39335 Email: st-studiensekretariat@uk-erlangen.de Dipl. Biol. Atefeh Nateghian Office for Clinical Studies Dept. of Radiation Therapy and Oncology University Hospital Frankfurt/M. Theodor-Stern-Kai 7 60590 Frankfurt Tel.: 069/6301-4655 Fax: 069/6301-4567 Email: studien-strahlen@kgu.de Dr. phil. nat. Margarita Diaz Maguina Office for Clinical Studies Dept. of Radiation Therapy and Oncology University Hospital Frankfurt/M. Theodor-Stern-Kai 7 60590 Frankfurt Tel.: 069/6301-3742 Fax: 069/6301-4567 Email: studien-strahlen@kgu.de
Participating Institutions:	cf. appendix

PROTOCOL APPROVAL / SIGNATURES

Date	Study Chairman

PROTOCOL APPROVAL / SIGNATURES BY LOCAL INVESTIGATOR

By signing this page, I agree

- to conduct the trial described in this protocol in compliance with GCP, with applicable regulatory requirements and with the protocol given approval by the Ethics Committee and the regulatory authority
- to comply with procedures for data recording and reporting (including data protection)
- to retain the trial-related essential documents as described in the protocol
- to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and European and national regulations governing the conduct of clinical studies.

Center	Local investigator (Print Name)
Date	Local investigator (Signature)

After signing this page, please fax or mail it to

Marga Lang-Welzenbach
Studiensekretariat
Strahlenklinik
Universitätsklinikum Erlangen
Universitätsstr. 27
91054 Erlangen
Tel.: 09131/85-33968
Fax: 09131/85-39335
Email: st-studiensekretariat@uk-erlangen.de

TABLE OF CONTENTS

Staffs and institutions with central responsibility: 2
Protocol approval / signatures 5
Protocol approval / signatures by Local Investigator 6
Table of contents 7
Table of appendices 10
Study synopsis 11
1 Scientific background and rationale for the study 16
1.1 Former clinical trials of the German Rectal Cancer Study Group 16
1.1.1 The medical problem 16
1.2 Induction chemotherapy prior to chemoradiotherapy and surgery 17
1.3 Optimal timing and sequence of induction chemotherapy, chemoradiotherapy and surgery 20
1.4 Rationale of the study 21
1.5 Study objectives 23
1.6 Primary objective 23
1.7 Secondary objectives 23
2 Study design 23
2.1 Type of study 23
2.2 Patient number 23
2.3 Time schedule 24
3 Patient selection 24
3.1 Inclusion criteria 24
3.2 Exclusion criteria 25
4 Treatment 27
4.1 Overview 27
4.1.1 Preoperative treatment in arm A 28
4.1.2 Preoperative treatment in arm B 28
4.2 Study medication 29
4.2.1 Distribution and accountability of study medication 29
4.2.2 General information on the study medication 29
4.2.3 Oxaliplatin 29
4.2.3.1 Formulation and administration 29
4.2.3.2 Handling precautions 29
4.2.3.3 Adverse events 30
4.2.4 5-Fluorouracil 30
4.2.4.1 Formulation and administration 30
4.2.4.2 Handling precautions 30
4.2.4.3 Adverse events 30
4.2.5 Folinic acid 31
4.2.5.1 Formulation and administration 31
4.2.5.2 Handling precautions 31
4.2.5.3 Adverse events 31
4.3 Radiotherapy 31
4.3.1 Technical Factors 31

4.3.2 Immobilization and Planning CT Scan....31
4.3.3 Target Volumes....32
4.3.4 Dose Prescription and Dose Specification....33
4.3.5 Documentation Requirements and Portal Films....33
4.3.6 Critical Normal Structures and Adverse events of Radiotherapy....33
4.3.7 Adverse events of Radiotherapy combined with 5-FU/Oxaliplatin....34
4.4 Surgery....34
4.5 Modifications of therapy and dosage....35
4.5.1 General remarks....35
4.5.2 Modifications of chemotherapy....35
4.5.2.1 General aspects....35
4.5.2.2 Precondition prior to every oxaliplatin administration (during RT or induction chemotherapy....35
4.5.2.3 Specific toxicities....36
4.5.3 Modifications of radiotherapy....38
4.6 Duration of study treatment....39
4.7 Concomitant and supportive treatment....39
4.7.1 General aspects....39
4.7.2 Treatment of nausea/vomiting....39
4.7.3 Treatment of diarrhea....40
4.7.4 Prevention and treatment of neutropenia....40
4.8 Emergency management....41
4.9 Patient registration and randomisation....41
4.10 Premature withdrawal of an individual subject - End of protocol specified therapy....42
4.11 Premature study termination by the sponsor and the coordinating investigator 42
5 Translational Program....43
6 Study assessments and criteria of evaluation....44
6.1 Overview / schedule of study assessments....44
6.2 Assessments at recruitment....47
6.3 Assessments during and after study treatment....48
6.3.1 Assessments during chemotherapy....48
6.3.2 Assessments during chemoradiotherapy....49
6.3.3 Assessments before surgery....49
6.3.4 Assessments after surgery....49
6.3.5 Follow-up procedures....50
6.4 Criteria for efficacy evaluation....50
6.4.1 Clinical/imaging tumor evaluations....50
6.4.2 Pathological tumor evaluations....51
6.4.3 Disease-free survival....51
6.4.4 Overall survival....52
6.4.5 Locoregional failure....52
6.4.6 Sphincter preservation rate....53
6.5 Criteria for safety evaluation....53
6.5.1 Toxicity / adverse events (AE)....53
6.5.2 Serious adverse events (SAE) / SUSAR....54

6.5.3 Methods of recording and assessing adverse events 55
6.5.4 Monitoring of subjects with adverse events 57
6.5.5 Procedure for reporting serious adverse events 58
6.5.6 Pregnancy Reporting 58
6.5.7 Overdose 59
7 Statistical aspects....59
7.1 General design....59
7.2 Sample size calculation 59
7.3 Evaluation categories of patients....60
7.4 Statistical methods....60
7.5 Adaptive procedures / interim and final analyses....61
8 Study documentation and archiving 61
8.1 Documentation and information flow....61
8.2 Data archiving....61
9 Financing....62
10 Use of information and publication 62
11 Ethical and legal requirements 62
11.1 General requirements and agreements....62
11.2 Declaration of helsinki 63
11.3 Informed consent of the patient 63
11.4 Quality assurance....64
11.4.1 Standardisation....64
11.4.2 Monitoring / source data verification....64
11.4.3 Audits....65
11.5 Registration and request for authorisation of the trial 65
11.6 Ethical committee....65
11.7 Protocol amendments 66
11.8 Subject insurance....66
11.9 Information on study drug to trial investigators 67
11.10 Data safety and monitoring board - DSMB 67
12 References 68
13 Appendices 70

TABLE OF APPENDICES

1. Patient information and patient informed consent form for the study and patient information consent form for the translational program
2. Performance status scale (ECOG)
3. NCI CTCAE v.4.0
4. SmPC
5. Subject insurance
6. Participating institutions
7. SOP Radiotherapy
8. SOP Histopathology
9. SOP MR Image Acquisition
10. Declaration of Helsinki

STUDY SYNOPSIS

Title of Study	**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**
Sponsor	Dean of the Medical Faculty, Goethe-University of Frankfurt
Study Chairman (LKP)	Prof. Dr. Claus Rödel, Frankfurt, for the German Rectal Cancer Study Group (CAO/ARO/AIO)
Rationale	Preoperative 5-FU-based chemoradiotherapy (CRT), total mesorectal excision surgery, and 4 cycles of adjuvant 5-FU – as established by CAO/ARO/AIO-94 – is at present a standard of care for patients with locally advanced rectal cancer (UICC stage II and III). The phase III German CAO/ARO/AIO-04 trial showed, that the addition of oxaliplatin increased treatment efficacy in terms of early secondary efficacy endpoints (e.g. the pCR-rate). With a median follow-up of 50 months, the primary endpoint of this trial - disease free survival - was significantly improved in the oxaliplatin-containing treatment arm (3-year DFS 71.2% versus 75.9%, HR 0.79, 95% CI 0.64-0.98, p=0.03). The hereby proposed randomized phase II trial CAO/ARO/AIO-12 aims at finding novel and innovative aspects of rectal cancer treatment, and will thus provide important information for defining the experimental arm in the upcoming large scale trial of the group. Compared to the current standard, in both study arms, the sequence of the three treatment modalities is modified, placing the chemotherapy block before surgery. The pre-operative sequence of chemotherapy → chemoradiotherapy (arm A) has been shown to be feasible with no early tumor progression prior to definitive surgical resection in a small randomized phase II study from Spain. The sequence chemoradiotherapy→ chemotherapy (arm B) may be beneficial according to response kinetics considerations, and by maintaining a highly effective local treatment in the first place. Both approaches could avoid the problem of major compliance problems with post-operative adjuvant chemotherapy.
Study type and study design	Investigator-driven, multicenter, explorative, open, randomized phase II study
Primary objective and endpoint	The primary objective of the study is 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 response (pCR, ypT0N0) will be compared exploratively between the treatment arms and to expectations

	derived from historical data.
Secondary objectives and endpoints	• Safety of the respective combination sequences (Toxicity assessment according to NCI CTCAE V.4.0) • Surgical morbidity and complications • Pathological staging, tumor downstaging (assessed by ypTNM findings in relation to initial cTNM staging), tumor regression grading according to Dworak • R0 resection rate; negative circumferential resection rate • Rate of sphincter-sparing surgery • Relapse-free survival (local / distant / overall) • Overall survival • Translational / biomarker studies
Inclusion criteria	• 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) • Staging requirements: High-resolution, thin-sliced (i.e. 3mm) magnetic resonance imaging (MRI) of the pelvis is the mandatory local staging procedure. • MRI-defined inclusion criteria: presence of at least one of the following high-risk conditions: o any cT3 if the distal extent of the tumor is < 6 cm from the anocutaneous line, or o cT3 in the middle third of the rectum (≥ 6-12 cm) with MRI evidence of extramural tumor spread into the mesorectal fat of more than 5 mm (>cT3b), or o resectable cT4 tumors, or o any clear cN+ based on MRI-criteria (see appendix) • Trans-rectal endoscopic ultrasound (EUS) is additionally used when MRI is not definitive to exclude early cT1/T2 disease in the lower third of the rectum or early cT3a/b tumors in the middle third of the rectum. • Spiral-CT of the abdomen and chest to exclude distant metastases. • Aged at least 18 years. No upper age limit. • WHO/ECOG Performance Status ≤1 • Adequate haematological, hepatic, renal and metabolic function parameters: o Leukocytes ≥ 3.000/mm^3, ANC ≥ 1.500/mm^3, platelets ≥ 100.000/mm^3, Hb > 9 g/dl o Serum creatinine ≤ 1.5 x upper limit of normal o Bilirubin ≤ 2.0 mg/dl, SGOT-SGPT, and AP ≤ 3 x upper limit of normal • Informed consent of the patient
Exclusion criteria	• Lower border of the tumor localised more than 12 cm from

	the anocutaneous line as measured by rigid rectoscopy • Distant metastases (to be excluded by CT scan of the thorax and abdomen) • Prior antineoplastic therapy for rectal cancer • Prior radiotherapy of the pelvic region • Major surgery within the last 4 weeks prior to inclusion • Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment. • Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 6 months (male or female) after the end of treatment (adequate: oral contraceptives, intrauterine device or barrier method in conjunction with spermicidal jelly). • On-treatment participation in a clinical study in the period 30 days prior to inclusion • Previous or current drug abuse • Other concomitant antineoplastic therapy • Serious concurrent diseases, including neurologic or psychiatric disorders (incl. dementia and uncontrolled seizures), active, uncontrolled infections, active, disseminated coagulation disorder • Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 6 months before enrolment. • Chronic diarrhea (> grade 1 according NCI CTCAE) • Prior or concurrent malignancy ≤ 3 years prior to enrolment in study (Exception: non-melanoma skin cancer or cervical carcinoma FIGO stage 0-1), if the patient is continuously disease-free • Known allergic reactions on study medication • Known dihydropyrimidine dehydrogenase deficiency • Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule (these conditions should be discussed with the patient before registration in the trial).
Treatment	In arm A patients receive pre-surgical induction chemotherapy with 5-FU/folinic acid/oxaliplatin followed by radiochemotherapy incorporating 5-FU and oxaliplatin. In arm B, the same treatment modalities are administered in reverse order. Cf. the flow chart in section 5.1 for a detailed overview.
Translational research	An extensive translational research program is implemented in order to further refine prognostic and predictive profiling, and eventually identifying subgroups which may be candidates for more conservative surgical procedures.

Sample size and justification	A total of 304 patients will be randomized to the two treatment arms with a randomization ratio of 1:1 (152 patients per group). Since the primary endpoint pathological complete response is assessed at surgery, only a small dropout of about 5% is expected, which results in an expected sample size of 144 patients per group. This sample size is sufficient to provide 80% power at an exploratory significance level of 20% (two-sided), assuming that pCR rates for induction CT followed by CRT, or CRT followed by induction CT, respectively, might be improved to about 25% compared to the 15% achieved by the currently standard treatment strategy. Comparing a pCR rate estimated from this trial with a fixed rate of say 15% at a significance level of 10% (one-sided) has a power of 95% assuming a trial pCR rate of 25% given the sample size of 144 patients per group. The power reduces to 87% when the usual two-sided significance level of 5% is used. The sample size gives a probability of 98% (92%) to pick the better treatment regimen for phase III evaluation assuming the pCR rates are 15% (18%) and 25%.
Biostatistical methods	All primary analyses will follow the ITT principle, i.e. all randomized patients will be included in the analyses and in the treatment groups they were randomized to. For the primary efficacy outcome, the proportions of patients with pCR will be reported with 95% confidence intervals and the treatment groups will be compared in a logistic regression with pCR as dependent variable and treatment and stratification parameters as factors. The odds ratio describing the treatment effect will be reported with 95% confidence intervals and p-value testing the null hypothesis of no effect. Time-to-event data such as recurrence-free survival and overall survival will be displayed by treatment group as Kaplan-Meyer curves with 95% confidence bands. The treatment effect will be estimated, if appropriate, as a hazard ratio in proportional hazards regression model with treatment and stratification parameters as factors. The hazard ratio will be reported with 95% confidence interval and p-value testing the null hypothesis of no effect. Dropout will be dealt with as independent right censoring.
Planned interim analyses	No formal interim analyses are planned. Standard safety follow-up will be conducted by an independent data monitoring committee.
Estimated number of sites	approx. 25 centers
Study duration	Start of preparation: Q3 2014 Start of recruitment: Q4 2014 Planned termination of recruitment: Q4 2016

	Planned termination of treatment/follow-up: Q4 2021 Final study report: Q1 2022

1 SCIENTIFIC BACKGROUND AND RATIONALE FOR THE STUDY

1.1 FORMER CLINICAL TRIALS OF THE GERMAN RECTAL CANCER STUDY GROUP

Radiotherapy, chemotherapy and surgical resection are important elements of multimodality treatment for patients with locally advanced rectal cancer. The optimum sequence and combination of these modalities has been addressed in several randomized trials, and preoperative combined chemoradiotherapy (CRT) has been shown to be superior to postoperative treatment for a variety of endpoints.[1,2] Following the publication of the landmark phase III intergroup trial of the German Rectal Cancer Study Group (CAO/ARO/AIO-94) in 2004, preoperative CRT has become standard of care for locally advanced rectal cancer in Germany, most parts of Europe and the United States.[2] This trial showed that with optimized local treatment, achieved by preoperative 5-flurouracil based CRT and total mesorectal excision (TME) surgery, local recurrence rates are less than 10%. It also became clear, however, that the development of distant metastases is now the predominant mode of failure in rectal cancer (25-30%), and any improvement in overall survival rates will require better control of systemic disease while keeping the rate of locoregional recurrences clearly below 10%. Thus, integrating more effective systemic therapy into combined modality programs has been the challenge.

Newer generation chemotherapeutics, such as oral fluoropyrimidines and oxaliplatin as well as molecularly targeted agents have subsequently been incorporated by the German Rectal Cancer Study Group within several phase I-II trials of preoperative CRT (for detailed reviews:[3,4]).[5-7] Recently, a phase III trial of our group (CAO/ARO/AIO-04) has been successfully completed accrual with more than 1250 patients recruited.[8] This phase III trial randomized patients either to the best arm of the former CAO/ARO/AIO-94 trial, i.e. 5-FU-based preoperative CRT, surgery, and 4 cycles of postoperative bolus 5-FU chemotherapy, or to the investigational arm, that incorporated oxaliplatin both into preoperative CRT as well as postoperative adjuvant chemotherapy. The primary endpoint of CAO/ARO/AIO-04 is disease-free survival. With a median follow-up of 50 months, this primary endpoint was significantly improved in the oxaliplatin-containing treatment arm (3-year DFS 71.2% versus 75.9%, HR 0.79, 95% CI 0.64-0.98, p=0.03).[9]

1.1.1 The medical problem

Given the fact, that the cumulative doses of the new drugs reached during preoperative CRT are substantially lower than in adjuvant colon cancer trials and probably not able to sufficiently reduce distant metastases, the question that needs to be addressed is how and when to apply systemic treatment with adequate dose and intensity. A recent randomized trial (CHRONICLE) investigated postoperative chemotherapy with capecitabine and oxaliplatin versus observation only after preoperative 5-FU-based CRT, however, this trial has unfortunately been closed due to poor accrual.[10] Two multicenter phase II trial (the CORE-study, and a phase II

study from the German Rectal Cancer Study Group) have investigated the feasibility of preoperative concomitant CRT with capecitabine and oxaliplatin (CAPOX) plus 4-6 cycles of adjuvant CAPOX chemotherapy following resection.[6,11] The most important finding of our German phase II trial was that less than 60% of the entire cohort of 103 operated patients were able to complete all 4 postoperative CAPOX cycles (with or without dose reduction); 27% did – for different reasons - not receive any adjuvant chemotherapy. The CORE-study reported similar figures with 35% of patients not receiving any adjuvant CAPOX, and further 14% of patients that stopped adjuvant chemotherapy prematurely. Thus, it is evident that preoperative CRT, surgical complications, and the fact that a substantial part of patients will have pathological complete response or yTNM stage I and II tumors due to downstaging effects, compromise the possibility and willingness of patients (and physicians) to tolerate (or recommend) postoperative chemotherapy.

1.2 INDUCTION CHEMOTHERAPY PRIOR TO CHEMORADIOTHERAPY AND SURGERY

In order to be able to apply chemotherapy with sufficient dose and intensity, an innovative approach is to deliver systemic therapy prior to preoperative CRT and surgery rather than as postoperative therapy. Although this strategy may be associated with its own caveats, such as selection of radio-resistant clones, induction of accelerated repopulation, possibly reduced compliance to CRT, and a substantial delay of definitive surgery, clinical results of phase II trials demonstrated the feasibility of this approach and provided promising first results (Table 1).[12-16] The largest series of Chau and colleagues (first published 2006 with 77 patients, updated 2010 with 105 patients) examined the use of 4 cycles of induction capecitabine plus oxaliplation (CAPOX) followed by CRT with capecitabine.[12,13] These authors reported a 20% pCR rate for patients with magnetic resonance imaging (MRI)-defined poor-risk tumors. Since there is an almost 6 month interval between diagnosis and surgery the radiologic response rate was followed by MRI. After induction chemotherapy the overall response rate was 74% which increased to 89% following the completion of CRT; no patient had progressive disease during neoadjuvant treatment.

Table 1: Phase II studies with induction chemotherapy (ICT) prior to preoperative chemoradiotherapy (CRT) with or without adjuvant chemotherapy (ACT) in rectal cancer patients

Series	N	Inclusion criteria	Treatment	Toxicity/Surgical Morbidity	Response	Comments
Chau et al. 2003	36	T3/T4 Nx/+ M0	Induction CT (ICT): 5-FU 300 mg/m² 12 wks, MMC 7 mg/m² every 6 weeks CRT: Starting wk 13, 5-FU 200 mg/m² during RT 50.4-54 Gy Surgery: 4-6 wks after CRT Adjuvant (ACT): 5-FU 300 mg/m² 12 wks, MMC 7 mg/m² every 6 weeks	ICT: G3/4: 25% CRT: G3/4 28% (skin) Surgery: 1 death (anastomotic leak with multiorgan failure), 5 further complications	ICT: 1 CR, 9 PR, 26 SD, 0 PD Objective response: 28% CRT: 6 CR, 23 PR, 5 SD, 2 PD Objective response: 81% Surgery: 1 pCR, 82% R0	22-24 weeks from start of treatment to surgery: 2 developed M1 before surgery
Chau et al. 2006; (updated Chua et al. 2010)	105	MRI-defined poor-risk: ≤ 1mm to mesorectum; T3 at/below levators; T3 ≥ 5 mm into fat; T4; N2; M0	ICT: Capecitabine 1000 mg/m² bid 14 days every 3 weeks, Oxaliplatin 130 mg/m² on day 1; 4 cycles CRT: Starting week 13, Capecitabine 825 mg/m² bid during RT 54 Gy Surgery: 6 weeks after CRT ACT: Capecitabine 1250 mg/m² bid 14 days every 3 weeks, 4 cycles	ICT: 5 deaths (2 pulmonary embolism , cardiac failure, myocardial infarction, neutropenic colitis), bowel perforation (n=1), small-bowel obstruction (n=1); G3-5 diarrhea 10%. CRT: G3-5: 42% skin Surgery: no deaths within 30 days	ICT: 3 CR, 75 PR, 16 SD, 0 PD Objective response: 74% CRT: 15 CR, 78 PR, 4 SD, 0 PD Objective response: 89% Surgery: pCR 20%; 5-year progression-free survival: 64%	22-24 weeks from start of treatment to surgery: no PD. After amendment for cardiovascular safety, only one further fatal pulmonary embolism
Calvo et al. 2006	52	T3/T4 or N+ M0	ICT: Oxaliplatin 85 mg/m² on day 1; 5-FU 400 mg/m² bolus d1, followed by 600 mg/m² continuous infusion in 22h with LV (200 mg/m²) d1-2, every 15 days, 2 cycles CRT: Starting after completion of the second FOLFOX4 course, Tegafur 400 mg given orally 3 times a day from d1-28 of RT 45-50.4 Gy Surgery: 4-6 weeks after CRT + IORT-Boost (10-15 Gy) ACT: Left to the treating oncologist's discretion	ICT: G3: 6% CRT: G3-4: 33% Surgery: 31% postoperative complications	ICT: not given CRT: not given Surgery: ypT0: 29%	14-16 weeks from start of treatment to surgery. If compared to 62 pts treated with the same CRT without ICT, no more tox., but more ypT0 (29% vs. 8%, p=0.006).
Koeberle et al. 2008	60	T3/T4 Nx/+ M0	ICT: Capecitabine 1000 mg/m² bid 14 days, Oxaliplatin 130 mg/m² day 1; 1 cycle CRT: Starting day 22, Capecitabine 825 mg/m² bid, d22-35 and d43-56, Oxaliplatin 50 mg/m² d 22,29,43,50 during RT 45 Gy Surgery: 5-6 weeks after CRT ACT: Left to the treating oncologist's discretion	ICT: G3 17% diarrhea, 3% G4 infection, 1/60 died 19 days after start of CT due to neutropenic sepsis CRT: G3 17% diarrhea. Surgery: not given	ICT: not given CRT: not given Surgery: ypT0N0: 23%	13-14 weeks from start of treatment to surgery.
Gunnlau-gsson et al. 2009	49	"Non-resectable" colorectal carcinoma T4NxM0-1; 41 pts rectal	ICT: Capecitabine 1000 mg/m² bid 14 days every 3 wks, Oxaliplatin 130 mg/m² day 1; 2 cycles CRT: Starting week 7, Capecitabine 825 mg/m² bid, Oxaliplatin 60 mg/m² weekly during RT 50,4 Gy Surgery: performed, if feasible	ICT: G3/4: 11% diarrhea CRT: G3/4: 24% diarrhea. 1 pts died due to myocardial infarction	ICT: not given CRT: 62% CR or PR Surgery: 38/49 pts received surgery; ypT0N0: 13%	Only 15% of the pts obtained all CT cycles without any dose reduction

Recently, a Spanish randomized phase II trial was reported comparing the induction chemotherapy approach with conventional preoperative CRT followed by surgery and postoperative chemotherapy (Table 2).[17] A total of 108 patients received preoperative 50.4 Gy plus CAPOX and were randomized to receive 4 months of CAPOX either by induction or adjuvant. Notably, all 54 patients that commenced induction chemotherapy also received CRT and underwent surgery. Although the pCR rates, downstaging and tumor regression grading were similar, both grade ≥3 toxicity was lower (19% vs. 54%, p=0.0004) and the ability to receive all 4 chemotherapy cycles was higher (92% vs. 57%, p=0.0001) with the induction approach. Whether or not this improvement in applicability and dose-density of chemotherapy will ultimately translate into improved disease-free survival will have to be tested in a larger phase III trial.

Grupo Cancer de Recto 3 Study	Induction-CAPOX + CRT+TME	CRT+TME + adjuvant CAPOX	p-value
Number of patients	56	52	
Efficacy			
pCR (primary endpoint)	14%	13%	0.94
Downstaging	43%	58%	0.13
R0 resection rate	86%	87%	0.4
18-months failure-free survival	76%	82%	0.39
Compliance			
Completion of treatment per protocol	91%	54%	<0.0001
Compliance to induction/adjuvant CT Received 0/≤2/3/4 cycles	0/1/2/51	12/7/2/28	0.0001
Compliance to CT during CRT Reveived 0/3/4/5 cycles	1/5/6/42	0/0/3/46	0.0502
Global relative dose intensity Capecitabine/Oxaliplatin/RT	0.91/0.94/0.94	0.67/0.73/0.96	CT<0.001 RT 0.9
Toxicity			
Any grade 3/4 induction/adjuvant CT	19%	54%	0.0004
Any grade 3/4 CRT	23%	29%	0.36
Any surgical complications	45%	51%	0.3
Death	6% (n=3; mesenteric thrombosis, mycocardial infarction, suicide)	6% (n=3; anastomitic leak in 2 cases, major depression)	1

Table 2: Results of the randomized phase II Grupo Cancer de Recto (GCR) 3 trial of induction versus adjuvant CAPOX in patients with rectal cancer

Indirect evidence that an improvement of DFS may indeed be achievable by induction chemotherapy before CRT comes from the recently published NSABP R-03 phase III trial.[1] The design of this trial was similar to the German CAO/ARO/AIO-94 and was launched to demonstrate that preoperative CRT is superior to postoperative CRT. A total of 267 patients was accrued between 1993 and 1999, when the trial was prematurely terminated because it did not meet the target accrual of 900 patients. Unlike the German trial, preoperative treatment consisted of induction chemotherapy (6 weeks of 5-FU/folinic acid) followed by CRT (50.4 Gy plus 5-FU/LV in the 1st and 5th week of RT) and surgery plus four adjuvant cycles of 5-FU/LV). The primary end points of this study were disease-free survival (DFS) and overall survival. The median follow-up time for surviving patients was 8.4 years. In contrast to the German trial, the 5-year DFS was significantly improved for patients treated with preoperative compared with postoperative therapy (65% versus 53%, p=0.011). As the 5-year cumulative incidence of locoregional recurrence was 10.7%

in each arm, it is tempting to speculate that the early onset of induction chemotherapy may have contributed to reduce distant recurrences in this trial.

1.3 OPTIMAL TIMING AND SEQUENCE OF INDUCTION CHEMOTHERAPY, CHEMORADIOTHERAPY AND SURGERY

The most commonly used time interval between completion of preoperative CRT and surgical resection has traditionally been 4-6 weeks. The Lyon R90-01 study was the only randomized trial in which patients with locally advanced rectal cancer treated with preoperative RT (39 Gy in fractions of 3 Gy) were randomly assigned to have surgery at two different time intervals following RT: at 2 weeks or after 6-8 weeks.[18] The longer interval resulted in a higher response rate compared to the 2-week interval (pathologic downstaging 10.3% vs. 26%, p=0.005). Several retrospective series have addressed the time interval as predictor of tumor response, surgical morbidity, and long-term outcome. In a series of 132 patients with locally advanced rectal cancer, Tulchinsky et al. found that patients operated on more than 7 weeks after CRT had similar rates of perioperative complications as compared to patients operated on less than 7 weeks after CRT, however, the longer CRT-to-surgery interval was associated with significantly improved pCR rates (35% vs. 17%, p=0.03) and significantly better disease-free survival.[19] These results were supported by Kalady et al. who found a 31% pCR rate in patients receiving surgery more than 8 weeks after CRT compared to 16% in patients operated on within 8 weeks of CRT.[20]

As these retrospective studies suggested an improved response with an interval longer than 6 weeks after completion of CRT, with no tumor progression during this period and no negative impact on surgical operability after the longer interval, several groups used this prolonged interval between CRT and surgery for adding chemotherapy. The *Timing of Rectal Cancer Response to Chemoradiation Consortium* in the United States (Julio Garcia-Aguilar et al., ClinicalTrials.org Identifier: NCT00335816) designed a prospective phase II trial of preoperative CRT (50.4 - 54Gy with 225 mg/m²/day continuous infusion 5-FU during RT) with 2 additional cycles of chemotherapy (modified FOLFOX6) during the waiting period before surgery (total time between completion of CRT and surgery: 11-13 weeks, i.e. 4 weeks between CRT and mFOLFOX6, 4 weeks for 2 cycles chemotherapy, and 3-5 weeks between end of mFOLFOX6 and surgery). The pCR rate in 70 patients treated within this study was 25% without an apparent increase in surgical complications if compared to former studies of the same group without additional chemotherapy during the waiting period.[21] Habr-Gama et al. treated 29 rectal cancer patients with 5-FU-based CRT (total dose of RT: 54 Gy) followed by 3 additional cycles of bolus 5-FU over 9 weeks. Tumor response was assessed by clinical examination (digital rectal, proctoscopy, endorectal ultrasound, MRI) 10 weeks after completion of CRT. In this series, a total of 22 of 29 patients (76%) had a complete clinical response and did not undergo initial surgery; 19 patients (65.5%) had a sustained clinical complete response after 12 months of follow-up.[22]

1.4 RATIONALE OF THE STUDY

Preoperative 5-FU-based CRT combined with TME surgery approximately 6 weeks after completion of CRT and 4 cycles of adjuvant 5-FU – as established by CAO/ARO/AIO-94 – is at present the standard of care for patients with locally advanced rectal cancer. The German CAO/ARO/AIO-04 trial, that incorporated oxaliplatin into the combined modality treatment, completed its accrual goal of 1250 patients in April 2010. First results on secondary endpoints, such as treatment compliance, acute toxicity, surgical and pathological parameters have been recently reported. Increased tumor response (pCR-rates) to neoadjuvant CRT with 5-FU/oxaliplatin compared to CRT with 5-FU alone was demonstrated without any higher acute toxicity.[8] With a median follow-up of 50 months, this primary endpoint was significantly improved in the oxaliplatin-containing treatment arm (3-year DFS 71.2% versus 75.9%, HR 0.79, 95% CI 0.64-0.98, p=0.03).[9] The hereby proposed randomized phase II trial CAO/ARO/AIO-12, incorporates novel and innovative aspects of rectal cancer treatment, and will thus provide important information for upcoming larger scale trials:

- Induction chemotherapy prior to preoperative CRT and surgical resection has been shown to be feasible with no early tumor progression prior to definitive surgical resection, no increase in perioperative morbidity, but with improved compliance and dose-density of chemotherapy. More data, however, is needed whether or not this approach is applicable in a multicenter setting within our German Rectal Cancer Study Group.
- An emerging body of data suggests that – reminiscent to anal cancer treatment - the response to CRT in patients with rectal cancer is time-dependent, and optimal local tumor regression may well take longer than the standard 6 weeks to surgery. Thus extending the interval between CRT and surgery may increase the proportion of patients achieving a pCR (and possibly thereby also improving disease-free survival). Moreover, this study will add valuable information to the aspect of future surgical treatment stratification, as several studies are now investigating a change in surgical approach for patients with tumors that respond completely to CRT.
- A further innovative aspect of this randomized phase II trial is the use of chemotherapy in the (prolonged) waiting period between completion of CRT and surgical resection. With this approach, effective local CRT is not postponed (and thus, progression of the primary tumor is unlikely) and the efficacy of CRT is not compromised by (possible) adverse events of induction chemotherapy, such as induction of accelerated repopulation, selection of resistant clones, among others.[23] Moreover, systemic chemotherapy after CRT but before surgery can likely be applied in adequate dose and intensity as it is not compromised by concomitant RT or postoperative complications.

Thus, we designed a randomized phase II trial that – in an ongoing tradition of our German Rectal Cancer Study Group – only alters the sequence of innovative

treatment components in order to improve treatment compliance and efficacy. The CRT regimen is identical to our former CAO/ARO/AIO-04 trial, i.e., it incorporates 5-FU continuous infusion and oxaliplatin. Based upon our experience with CAO/ARO/AIO-04, this CRT regimen is associated with high treatment compliance and modest acute toxicity (which was not significantly different from the standard 5-FU CRT regimen), but exerted increased tumor response.[8] The chemotherapy part (modified FOLFOX6) is also identical to CAO/ARO/AIO-04, however, the number of cycles has been reduced to 3, owing to the facts that (a) surgery should not be postponed longer than approximately 120 days after start of treatment, (2) the cumulative dose of oxaliplatin applied preoperatively together with CRT amounts to 500 mg/m².

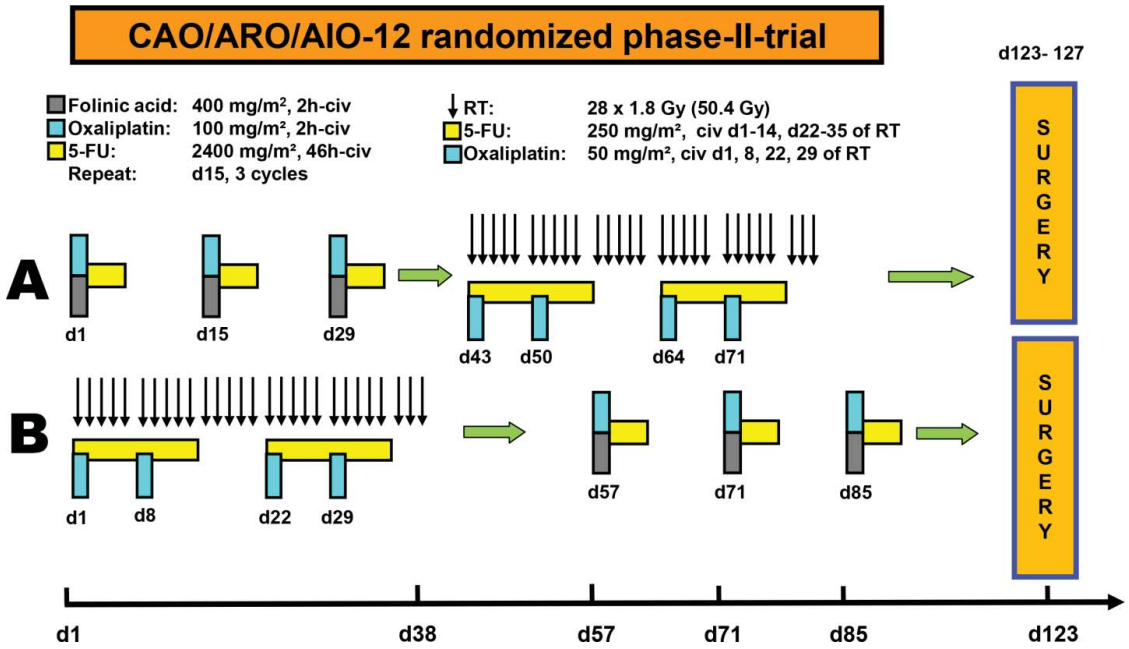

Fig. Study overview / therapy flowsheet

1.5 STUDY OBJECTIVES

1.6 PRIMARY OBJECTIVE

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

1.7 SECONDARY OBJECTIVES

Secondary endpoints to be analysed:

- Safety of the respective combination sequences (toxicity assessment according to NCI CTCAE Version 4.0)
- Surgical morbidity and complications
- Pathological staging, tumor downstaging (assessed by ypTNM findings in relation to initial cTNM staging), tumor regression grading according to Dworak
- R0 resection rate, rate of circumferential resection margin negativity (> 1mm)
- Rate of sphincter-sparing surgery
- Relapse-free survival (local / distant / overall)
- Overall survival
- Translational / biomarker studies; cf. appendix for details

2 STUDY DESIGN

2.1 TYPE OF STUDY

Investigator-driven, multicenter, explorative, open, randomized phase II study

2.2 PATIENT NUMBER

304 patients evaluable for the primary endpoint are required (cf. chapter “Statistical Aspects” for details), assuming an uninformative drop-out rate of up to 5% with no reliable information on the primary endpoint.

Number of participating clinical centers: approx.25

2.3 TIME SCHEDULE

Start of preparation:	Q3 2014
Start of recruitment:	Q4 2014
Planned termination of recruitment:	Q4 2016
Planned termination of treatment/follow-up:	Q4 2021
Final study report:	Q1 2022

3 PATIENT SELECTION

3.1 INCLUSION CRITERIA

- Male and female patients with histologically confirmed diagnosis of rectal cancer localised 0 – 12 cm from the anocutaneous line as measured by rigid rectoscopy (i.e. lower and middle third of the rectum)
- Staging requirements: High-resolution, thin-sliced (i.e. 3mm) magnetic resonance imaging (MRI) of the pelvis is the mandatory local staging procedure.
- MRI-defined inclusion criteria: presence of at least one of the following high risk conditions:
    - any cT3 if the distal extent of the tumor is < 6 cm from anocutaneous line or
    - cT3 in the middle third of the rectum (≥ 6-12 cm) with MRI evidence of extramural tumor spread into the mesorectal fat of more than 5 mm (>cT3b), or
    - resectable cT4 tumors, or
    - any clear cN+ based on MRI-criteria (see Appendix).
- Trans-rectal endoscopic ultrasound (EUS) is additionally used when MRI is not definitive to exclude early cT1/T2 disease in the lower third of the rectum or early cT3a/b tumors in the middle third of the rectum.
- Spiral-CT of the abdomen and chest to exclude distant metastases.
- Aged at least 18 years. No upper age limit.
- WHO/ECOG Performance Status ≤ 1
- Adequate haematological, hepatic, renal and metabolic function parameters:
    - Leukocytes ≥ 3.000/mm^3, ANC ≥ 1.500/mm^3, platelets ≥ 100.000/mm^3, Hb > 9 g/dl
    - Serum creatinine ≤ 1.5 x upper limit of normal

  - Bilirubin ≤ 2.0 mg/dl, SGOT-SGPT, and AP ≤ 3 x upper limit of normal

- Informed consent of the patient

No study treatment or any other procedure within the framework of the trial (except for screening assessments) will be performed in any patient prior to receipt of written informed consent.

3.2 EXCLUSION CRITERIA

- Lower border of the tumor localised more than 12 cm from the anocutaneous line as measured by rigid rectoscopy
- Distant metastases (to be excluded by CT scan of the thorax and abdomen)
- Prior antineoplastic therapy for rectal cancer
- Prior radiotherapy of the pelvic region
- Major surgery within the last 4 weeks prior to inclusion
- Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment.
- Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 6 months (male or female) after the end of treatment (adequate: oral contraceptives, intrauterine device or barrier method in conjunction with spermicidal jelly).
- On-treatment participation in a clinical study in the period 30 days prior to inclusion
- Previous or current drug abuse
- Other concomitant antineoplastic therapy
- Serious concurrent diseases, including neurologic or psychiatric disorders (incl. dementia and uncontrolled seizures), active, uncontrolled infections, active, disseminated coagulation disorder
- Clinically significant cardiovascular disease in (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ≤ 6 months before enrolment.
- Chronic diarrhea (> grade 1 according NCI CTCAE)
- Prior or concurrent malignancy ≤ 3 years prior to enrolment in study (Exception: non-melanoma skin cancer or cervical carcinoma FIGO stage 0-1), if the patient is continuously disease-free
- Known allergic reactions on study medication
- Known dihydropyrimidine dehydrogenase deficiency

- Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule (these conditions should be discussed with the patient before registration in the trial).

4 TREATMENT

4.1 OF OVERVIEW

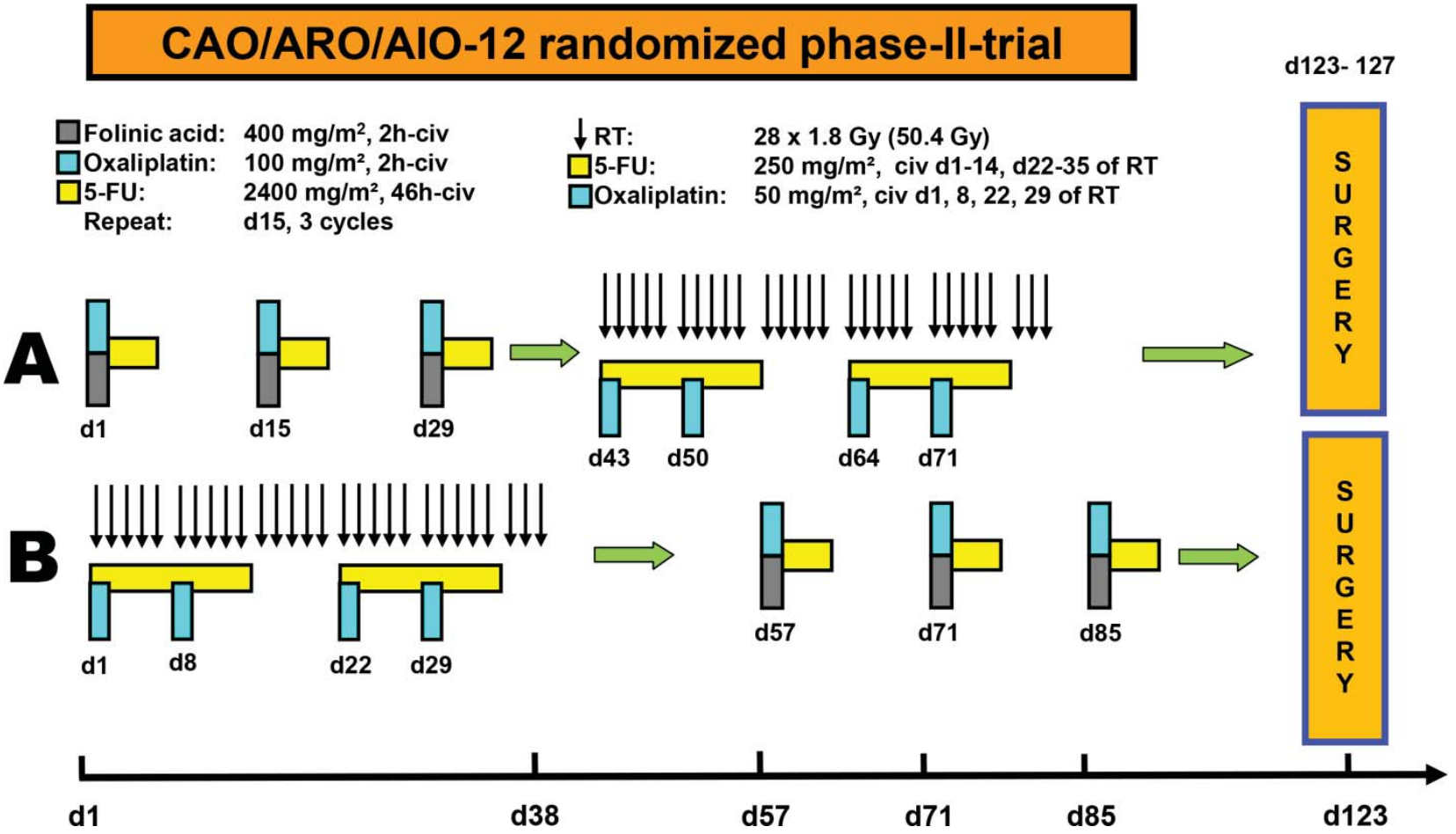

Fig.: Study Overview

4.1.1 Preoperative treatment in arm A

After randomisation, patients receive three induction chemotherapy cycles, starting on day 1, 15 and 29, consisting of

Folinic acid: 400 mg/m^2, 2h-civ

Oxaliplatin: 100 mg/m^2, 2h-civ

5-FU: 2400 mg/m^2, 46h-civ

After a break of two weeks (calculated from day 29, i.e. on day 43), chemoradiotherapy is started according to the following schedule:

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/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.

4.1.2 Preoperative treatment in arm B

After randomisation, chemoradiotherapy is started according to the following schedule:

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

After a break of two and a half weeks (after last radiation, i.e. day 38), patients receive induction chemotherapy cycles, starting on day 57, 71 and 85, consisting of

Folinic acid: 400 mg/m^2, 2h-civ

Oxaliplatin: 100 mg/m^2, 2h-civ

5-FU: 2400 mg/m^2, 46h-civ

Accordingly, induction chemotherapy should be finalized on day 85 (+1, due to the duration of 5-FU infusion), if no delays are required. Surgery should be performed about 5 weeks later, i.e. around day 123.

4.2 STUDY MEDICATION

4.2.1 Distribution and accountability of study medication

5-fluorouracil, folinic acid and oxaliplatin are generally available and a routine treatment schedule for advanced colorectal cancer. Thus, they will be prescribed by the treating physician, and not provided by the sponsor or any third party.

Thus, there are no requirements to maintain trial-specific records of the inventory at the site, the use for each subject, and the delivery, storage and destruction (i.e. no measures of drug accountability beyond the general routine practice in the respective institutions). By filling the CRF, the investigators adequately document that subjects were provided the doses specified in the protocol.

4.2.2 General information on the study medication

The relevant information on the drug characteristics, storage, application, mode of action and adverse reactions is included in the Summary of Product Characteristics (SmPC, “Fachinformation”, see appendix) for 5-FU, folinic acid and oxaliplatin. The attached versions of SmPC will be the directive standard for the evaluation of toxicity and relatedness. Only in case of major new findings that will affect the risk-benefit analysis, the SmPC will be updated.

All chemotherapy is administered on the basis of milligrams of drug per square meter of body surface area (BSA), up to a maximum of 2 m^2. For body surface area calculation the actual body weight will be used.

The BSA will be (re-)calculated on the following days, respectively on the start of the following cycles: Arm A: d1, d43, d64; Arm B: d1, d22, d57 or in case of severe weight loss.

4.2.3 Oxaliplatin

4.2.3.1 Formulation and administration

Oxaliplatin is presented as a clear, colorness solution packaged in glass vials of 10/20/40ml with oxaliplatin 50/100/200mg of active compound to be diluted for infusion.

Oxaliplatin will be administered in 250-500 ml of 5% glucose solution to the patient as a two hour i.v. infusion. Oxaliplatin should always be administered before 5-FU. For further information see the SmPC in the appendix.

4.2.3.2 Handling precautions

Oxaliplatin is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing oxaliplatin solutions. The use of gloves is recommended.

If oxaliplatin concentrate, reconstituted solution or infusion solution should come into contact with skin wash immediately and thoroughly with water. If oxaliplatin concentrate, premix solution or infusion solution should come into contact with mucous membranes wash immediately and thoroughly with water.

Do not combine with alkaline medications or media that cause oxaliplatin to degrade. Do not administer other agents simultaneously by the same line. Flush line after oxaliplatin administration before using the line to administer other agents. Do not use preparation or administration needles or intravenous sets containing aluminium components, as there is a risk of oxaliplatin degradation.

4.2.3.3 Adverse events

Adverse events include nausea, vomiting, diarrhea, stomatitis/mucositis, obstipation, leucopenia, thrombocytopenia, anemia, increase of liver enzymes, alopecia, peripheral neurotoxicity, head ache, dyspnea, coughing, epistaxis, infection, fatigue, fever, asthenia, allergic reaction.

Please refer to the SmPC (“Fachinformation”) in appendix for extensive information.

4.2.4 5-Fluorouracil

4.2.4.1 Formulation and administration

5-FU is available as 50 mg/ml aqueous solution, colorless to faint yellow. Administration of 5-FU should be only by the intravenous route taking care to avoid extravasation. Direct administration is over 1-2 minutes, or intermittently in a 50-100 ml minibag over 20-30 minutes, or (in this trial exclusively) by continuous infusion (in 1 L NS or ambulatory infusion pump, compatible with heparin and leucovorin but not with ondansetron) which has the best therapeutic index. Vein pigmentation and thrombophlebitis may be seen distal to infusion sites.

4.2.4.2 Handling precautions

5-FU is compatible with normal saline (NS) and dextrose 5% in water (D5W). Because of the mutagenic and carciogenic effects of 5-FU enhanced safety regulations are to be applied. The use of gloves is recommended.

4.2.4.3 Adverse events

Immediate side effects include mild nausea and vomiting (common), lacrimation, conjunctivitis, angina, arrhythmia, radiation recall and anaphylaxis(rare). Early onset effects include stomatitis and esophago-pharyngitis (which may lead to sloughing and ulceration), diarrhea with cramping and/or bleeding, and anorexia. Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first dose, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range. Megaloblastosis may occur. Alopecia (usually mild) and dermatitis may be seen. The dermatitis most often seen is a pruritic maculopapular rash usually

appearing on the extremities and less frequently on the trunk. Other side effects include myocardial ischemia, lethargy, malaise, headache, allergic reactions, neurotoxicity (disorientation, confusion, euphoria, dizziness, incoordination-acute cerebellar syndrome, encephalopathy), visual changes, photosensitivity (eyes and skin), nail changes including loss of nails, skin thickening, cracking, dryness or sloughing, biliary sclerosis, cystitis. Hand foot syndrome (palmar plantar erythrodysesthesia) is more common with continuous infusion. Late effects may include tear duct fibrosis and neurotoxicity.

4.2.5 Folinic acid

4.2.5.1 Formulation and administration

Folinic acid is presented as a clear to faint yellow solution with 10mg/ml folinic acid as calciumfolinat for infusion. For further information see the SmPC in the appendix.

4.2.5.2 Handling precautions

If the solution appears unclear or with particles, it has to be discarded properly.

4.2.5.3 Adverse events

Folinic acid is administered with 5-FU and may increase the toxic effects of 5-FU. Please refer to the SmPC (“Fachinformation”) in appendix for further details.

4.3 RADIOTHERAPY

4.3.1 Technical Factors

Radiotherapy can be given to the patients as three-dimensional planned radiotherapy (3-D RT), intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) and should be continued for the entire course of treatment. Megavoltage equipment equal to or greater than 6 MeV photons is mandatory. At least a three-field technique for 3-D RT, a multi-field technique for IMRT or a rotation technology for VMAT is necessary. A multi-leaf collimator is required to allow customized blocking and, if necessary, intensity modulation. The radiotherapy technique is chosen by the treating radiation oncologist on the basis of individual clinical factors (e.g. patient anatomy). However, IMRT or VMAT technique should be preferred, hence, in comparison with 3-D RT, the dosimetric improvements can result in significant lower exposure to the organs at risk.[24]

4.3.2 Immobilization and Planning CT Scan

The use of specific positioning devices to treat the abdominopelvic region is mandatory. We recommend treating the patient in prone position, if prone position is not feasible, the patient can be treated supine. Measures should be taken to reduce the exposure of the small bowel and in the case of male patients of the testes in the treatment field, e.g. by using a (double) belly board device or open table top device.

A treatment planning CT scan is mandatory for defining the target volume, CT scan thickness should preferably be 3 mm but not exceed 5 mm. The treatment planning CT scan must be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues receiving any irradiation must be included in the CT scan.

4.3.3 Target Volumes

On all appropriate CT slices, the gross target volume (GTV) and the clinical target volume (CTV) should be outlined. For the GTV, the primary lesion and suspect lymph nodes (defined on pre-treatment examinations including CT/MRI) should be delineated separately.

The CTV is designed to cover the tumor (GTV) with margin, mesorectal, presacral and internal iliac nodes. If the tumor extends to anterior organs (bladder, prostate, seminal vesicles, uterus, vagina) the affected parts of these organs should be included into the CTV. Furthermore, in those cases the external iliac nodes should be included in the CTV as well. Inguinal lymph nodes should be included in case of infiltration of the lower third of the vagina or the anal canal. If the patient is intended to undergo an abdominoperineal resection or the lesion is within 2 cm from the anal verge and the surgeon is planning a sphincter saving procedure, the anal sphincter complex needs to be included (at least partially) in the CTV. The rationale behind these delineation guidelines can be found in the article by Roels et al.[25] More details on contouring the respective target volumes can also be found within the SOP Radiotherapy (appendix).

In general, the whole pelvis field should have the superior border in L5-S1 if lymph nodes or the mesorectal fascia (MRF) are clearly found to be involved on pre-treatment MRI. The inferior border should be at least 3 cm below the primary tumor.

With regard to the superior border, Nijkamp et al. analysed in a recent study the incidence of recurrence in patients treated within the Dutch rectal cancer trial.[26] In patients with primary node-negative disease (cN0) without MRI-defined involvement of the mesorectal fascia, most cranial recurrences were located at or below the level of the S2–S3 interspace. The authors concluded that CTV can probably be reduced on the cranial side to the S2–S3 interspace in this patient subgroup (N0 disease and negative MRI-defined MRF) without significantly increasing the local recurrence rate. Importantly, with a cranially reduced CTV to the S2-S3 interspace, the small bowel exposure could be decreased by 60% and 80% using 3D-CRT and IMRT, respectively, and hence a lower toxicity can be expected. Hence, following that study and upon careful consideration of the current literature, the German Rectal Study group has decided to consider as cranial border for the CTV the S2-S3 interspace in the case of cN0 and MRF. The cranial border of the CTV should be extended above the S2-3 interspace, if necessary to achieve, a minimum 2 cm margin above the most superior aspect of GTV.

The Planning Target Volume (PTV) represents an additional margin around the CTV to compensate for the variability of treatment set up and internal organ motion. A

minimum margin of at least 0.5 cm around the CTV is required in all directions to define a respective PTV. Additional margins may be required based upon clinical judgment, especially in the case of suspected or diagnosed lymph node metastases. Examples for contouring the respective target volumes can also be found within the "Radiotherapy procedures" (appendix).

Organs at Risks (OAR): The small bowel is contoured from the Douglas pouch up to at least 1 cm above the cranial PTV margin. The whole bladder is outlined, whereas planning CT scan and radiotherapy are performed with full bladder. The rectum is contoured from the ischial tuberosities up to the flexion at the junction with the sigmoid. Furthermore, the anus and the testicles should be contoured.[27]

4.3.4 Dose Prescription and Dose Specification

The radiotherapy will be given in 28 fractions over approximately 5 and a half weeks. The total dose is 50.4 Gy in 1.8 Gy per day. The 3D RT dose will be defined at the ICRU 50 reference point. For IMRT and VMAT, the digital dose distribution should be defined according to the ICRU report 83 at the $D_{50\%}$.

Additionally:

- The isodose curve representing the 95% of the prescribed dose must encompass the entire PTV.
- No part of the PTV should receive ≥ 110% of the prescribed dose.
- Replacement of the PTV point dosages Dmin and Dmax by the volume based dosages D98% and D2% of the DVHs should be considered for all techniques
- Less than 1% or 1cc of the tissue outside the PTV should receive ≥ 110% of the prescribed dose to the PTV.

4.3.5 Documentation Requirements and Portal Films

Portal image of each field or orthogonal images that localize the isocenter placement must be obtained on the first day of therapy. Isodose plans, DVHs of the target volumes and critical normal structures are obligate for planning. Weekly positioning controls of the patients are required. Image guided radiotherapy (IGRT) with daily positioning control is allowed, but not mandatory.

4.3.6 Critical Normal Structures and Adverse events of Radiotherapy

Critical normal structures include the small bowel, bladder and rectum. Acute side effects such as skin toxicity, diarrhea, proctitis, and dysuria are common during treatment. These conditions are usually transient and resolve within a few weeks following the completion of CRT.

The most common delayed severe complications are due to small bowel damage and include small bowel enteritis, adhesions, and small bowel obstruction requiring surgical intervention. The incidence of small bowel obstruction requiring surgery was as low as 2% in the preoperative CRT arm of the recent German Rectal Cancer Study (CAO/ARO/AIO-94). Other delayed complications include: impairment of sphincter function, proctitis and strictures at the anastomotic site, perineal/scrotal tenderness, delayed perineal wound healing, urinary incontinence, bladder atrophy/bleeding, sexual dysfunction with possible long-term deterioration of ejaculatory and erectile function in men, and vaginal dryness and diminished sexual satisfaction in females.

4.3.7 Adverse events of Radiotherapy combined with 5-FU/Oxaliplatin

Based on our experience within the CAO/ARO/AIO-04 trial, using the identical regimen of 5-FU/Oxaliplatin-based chemoradiotherapy as proposed in this trial, we expect that the overall grade 3-4 acute toxicity from preoperative treatment with 5-FU/OX-CRT will be between 20-25%. Grade 3-4 gastrointestinal toxicity occurred in 20%, mostly due to diarrhea (12%) and nausea/vomiting (4%). Other grade ≥ 3 toxicities were infrequent. With a cumulative oxaliplatin dose of 200 mg/m² during preoperative CRT, grade ≥ 2 neuropathy was observed in only 11% of patients. Full dose of RT could be applied 94%, and full dose chemotherapy during RT in 85%.[8]

4.4 SURGERY

Rectal excision is usually performed with a midline incision but a laparoscopic approach is possible providing an adequate experience of the operative team. Abdominal cavity should be checked for the presence of peritoneal carcinomatosis or liver metastases. Biopsy of liver masses or peritoneal deposits is recommended.

Rectal resection should be done with complete TME according to the technique described by B. Heald.[28] Autonomic pelvic nerve preservation should be performed if permitted by tumor extension. Sphincter preservation should be attempted in every case even for tumors of the lower rectum providing that the sphincter is not involved and that a 2 cm free margin can be obtained below the lower edge of the tumor. If sphincter preservation seems oncologically safe but technically not feasible (i.e. preoperative incontinence, obesity, narrow pelvis, insufficient blood supply to the left colon) this should be noticed.

Restoration of bowel continuity can be done by either colorectal anastomosis, mechanical or handsewn coloanal anastomosis according to the length of rectal remnant and to the surgeon preference. In case of coloanal anastomosis the construction of a colic pouch or a side to end anastomosis, if technically feasible, is advised. A defunctioning loop ileostomy (or colostomy) should be done for low colorectal or coloanal anastomosis in order to prevent anastomotic leakage.

4.5 MODIFICATIONS OF THERAPY AND DOSAGE

4.5.1 General remarks

Toxicity will be graded according to NCI CTCAE, version 4.0 (see appendix); the therapy modifications described below are applied according to this severity grading.

Toxicities of severity grade 1 only will not lead to any dose reduction or cycle delay. The same holds for adverse reactions without any potential of serious or life-threatening complications according to the judgment of the physician (e.g. alopecia). Presumably, severe overlapping toxicity between radiotherapy and chemotherapy will not occur (except possibly for diarrhea). Thus, in case of toxicity requiring treatment modification, this alteration should reflect the causal relationship of the respective modality. E.g., if the toxicity is unequivocally caused by radiation only, a dosage modification of chemotherapy is not required.

If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification. Dose reductions once performed will remain effective for the rest of the pre-operative treatment. Each dose modification or treatment delay has to be documented in the CRF, including the respective reason.

If toxicity should require a treatment delay of more than 2 weeks, it is mandatory to contact the study chairman for further guidance.

4.5.2 Modifications of chemotherapy

4.5.2.1 General aspects

If oxaliplatin has to be stopped permanently, 5-FU should be applied as single drug at an unchanged dose level. This implies that the patient remains on study therapy. However, if 5-FU has to be stopped permanently, chemotherapy is discontinued completely, i.e. oxaliplatin is not given as monotherapy. Then, the patient is discontinued from study-specific treatment. It is mandatory that further treatment (e.g. surgery) and follow-up data are recorded, unless the patient withdraws his consent to do so.

4.5.2.2 Precondition prior to every oxaliplatin administration (during RT or induction chemotherapy

The following requirements have to be met, before every administration of oxaliplatin:

- No hematotoxicity of grade ≥ 2 (i.e. neutrophils > 1.500/mm^3, platelets > 75.000/mm^3)
- No stomatitis, nausea, vomiting, diarrhea, hand-foot syndrome ≥ 3
- No other non-hematological toxicity (except for alopecia) of grade ≥ 2
- Bilirubin ≤ 1.5 x UNL

- Transaminases ≤ 2.5 x UNL
- No cardiac toxicity
- No peripheral neurotoxicity ≥ 3
- Creatinine clearance ≥ 50 ml/min

If the pre-conditions for the start of a new course are not met, treatment should be delayed up to a maximum of 2 weeks. If toxicity requires a treatment delay of more than 2 weeks, it is mandatory to contact the study chairman for further guidance. **Chemotherapy during radiotherapy should be administered simultaneously, i.e. every effort should be done to apply all chemotherapy at the given timepoints during radiotherapy.**

4.5.2.3 Specific toxicities

The dose modifications provided in the following tables are recommended for the **subsequent** cycle.

Hematologic Toxicities

In the event of any pre-cycle haematology profile identifying neutropenia and or thrombocytopenia, treatment should be delayed until the absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 75 x 10^9/L, and recovery from non-haematological toxicity to baseline or grade ≤ 1. Treatment should then be re-initiated with the doses indicated in the tables below.

Modifications to the chemotherapy regimen due to NEUTROPENIA

CTCAE Grade	Grade 2	Grade 3	Grade 4
ANC Range	**≥ 1.0 to < 1.5 x 10^9/L**	**≥ 0.5 to < 1.0 x 10^9/L**	**< 0.5 x 10^9/L**
1st Occurrence	No dose adjustment	Cytotoxic drugs at 75% of initial dose. Consider prophylactic G-CSF	Cytotoxic drugs at 50% of initial dose. Consider prophylactic G-CSF
2nd Occurrence	No dose adjustment	Cytotoxic drugs at 50% of initial dose. Consider prophylactic G-CSF	Stop treatment permanently
3rd Occurrence	No dose adjustment	Stop treatment permanently unless it is in the subject's best interest to continue on 5-FU/leucovorin alone	Not applicable

Modifications to the chemotherapy regimen due to FEBRILE NEUTROPENIA

CTCAE Grade	Grade 3	Grade 4
ANC Range	**< 1.0 x 10^9/L**	**< 1.0 x 10^9/L**
Temperature	**≥ 38.5°C**	**≥ 38.5°C**
Life-threatening sepsis	**No**	**Yes**
1st Occurrence	Cytotoxic drugs at 75% of initial dose. In addition, consider prophylactic G-CSF	Stop treatment permanently unless it is in the subject's best interest to continue on 5-FU/leucovorin alone. Consider prophylactic G-CSF

2nd Occurrence	Stop treatment permanently unless it is in the subject's best interest to continue on 5-FU/leucovorin alone. Consider prophylactic G-CSF	Stop treatment permanently.

Modifications to the FOLFOX regimen due to THROMBOCYTOPENIA

Platelet Range	≥ 50 to < 75 x 10^9/L	≥ 25 to < 50 x 10^9/L	< 25 x 10^9/L
1st Occurrence	No dose adjustment	Cytotoxic drugs at 75% of initial dose	Cytotoxic drugs at 50% of initial dose
2nd Occurrence	No dose adjustment	Cytotoxic drugs at 50% of initial dose	Stop treatment permanently unless it is in the subject's best interest to continue on 5-FU/leucovorin alone
3rd Occurrence	No dose adjustment	Stop treatment permanently unless it is in the subject's best interest to continue on 5-FU/leucovorin alone	Stop treatment permanently.

Neurosensory toxicity

Oxaliplatin-related neurotoxicity is, in addition to the NCI CTC grading, recorded according to the scale defined by Wassermann (see following table).

Severity grading of peripheral neurotoxicity according to Wasserman

Grade 1	Paresthesia/dysesthesia duration ≤ 7 days
Grade 2	Paresthesia/dysesthesia duration 8-14 days
Grade 3	Paresthesia/dysesthesia duration > 14 days
Grade 4	Paresthesia/dysesthesia with functional impairment

It leads to the following dose modifications:

Modifications to the FU/oxaliplatin regimen due to PERIPHERAL NEUROTOXICITY

	Duration of toxicity		
	1 - 7 days	**> 7 days**	**Continuing between cycles**
Cold-related dysesthesia	No dose adjustment	No dose adjustment	No dose adjustment
Paresthesia	No dose adjustment	No dose adjustment	Dose: 75%
Paresthesia with pain	No dose adjustment	Dose: 75%	Stop oxaliplatin permanently; continue 5-FU
Paresthesia with functional impairment	No dose adjustment	Dose: 50%	Stop oxaliplatin permanently; continue 5-FU

In a small proportion of patients (1-2%) laryngopharyngeal dysesthesia, a special form of acute neuropathy, may occur, characterized by a subjective feeling of

dysphagia and dyspnoe, without any objective sign of breathing obstruction. This symptom is not life-threatening and quickly reversible without treatment. During the following cycles the infusion duration of oxaliplatin should be extended to 6 hours. The use of calcium and magnesium infusion in conjunction with oxaliplatin to prevent oxaliplatin-induced neurotoxicity is not recommended.

Diarrhea
If the patient develops a grade 4 diarrhea related to either radiation therapy or chemotherapy, all therapy must be held until the toxicity has resolved to ≤ grade 2. If the toxicity has not resolved to ≤ grade 2 after 2 weeks the study treatment should be discontinued and the patient treated at the discretion of the investigator. If toxicity requires a treatment delay or the interruption of the drugs of more than one week, the patient should complete radiation where possible and the be followed up.

Emesis
FOLFOX is known to be a moderate emetogenic treatment. To prevent acute and delayed chemotherapy-induced nausea and vomiting the use of a 5-HT3 anatgonist in combination with dexamethasone 8 mg day 1 followed by dexamethasone 8 mg days 2 and 3 is recommended.

Hypersensitivity reaction
In case of an allergic reaction to oxaliplatin, the re-introduction of the drug should be considered only in case of mild symptoms and based on individual risk assessment. Pre-medication with dexamethasone 20 mg IV, diphenhydramine 50 mg IV, and one of the following: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV 30 minutes prior to study drug administration is suggested. If an allergic reaction persists into the next cycle, administer 50 mg dexamethasone p.o. 12 hours and 6 hours prior to administration of oxaliplatin.

If a grade 3 or 4 toxicity occurs after two dose reductions the patient is taken off study-specific treatment. It is mandatory that further treatment (e.g. surgery) and follow up data are recorded unless the patient withdraws his consent to do so.

4.5.3 Modifications of radiotherapy

In case of diarrhea caused by radiotherapy or concurrent chemoradiotherapy, recommendations for treatment adjustment are provided in the table below. However, the definitive decision on any interruption or termination is up to the discretion of the treating radiooncologist.

Radiotherapy adjustments in case of gastrointestinal toxicity

Diarrhea toxicity grade (CTCAE)	Radiotherapy
1	continue
2	continue / loperamid support
3	Intermission of radiotherapy for a maximum of 7 days; if diarrhea is not responsive to anti-diarrhea treatment; if the severity persists after 7 days, termination of radiotherapy
4	Stop all radiochemotherapy; if the toxicity has not resolved to ≤ grade 2 after 2 weeks, the study treatment should be discontinued and the patient treated at the discretion of the investigator

4.6 DURATION OF STUDY TREATMENT

The total duration if preoperative therapy is 81 (Arm A) to 85 (Arm B) days, if no delay is required. Surgery should be performed 5 (Arm B) to 6 weeks (Arm A) after end of neoadjuvant treatment.

4.7 CONCOMITANT AND SUPPORTIVE TREATMENT

4.7.1 General aspects

In general, the patients should continue to take their previous therapies according to the recommendations of the responsible physician. The following concomitant therapies will not be allowed:

- any other antineoplastic treatment
- other investigational therapies

The relevant concomitant medication has to be recorded. Additionally, any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded.

Supportive care for treatment-related symptoms will be offered as needed to all patients in this study.

4.7.2 Treatment of nausea/vomiting

For nausea and vomiting, an oral 5-HT3 antagonist is the first option; metoclopramide, alizapride and prochlorperazine may be also used.

4.7.3 Treatment of diarrhea

Symptoms of diarrhea and/or abdominal cramping may occur at any time and should be managed according to standard institutional practice. A prophylactic medication is not recommended.

Subjects should be instructed to notify the investigator or nurse for the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, inability to control diarrhea (return to baseline) within 24 hours. Subjects with diarrhea should be evaluated frequently by a nurse or physician until resolution of diarrhea.

Changes in electrolytes, even without BUN/urea and/or creatinine elevation, may reflect early physiologic consequences of treatment-induced gastrointestinal toxicity. Subjects with clinically significant electrolyte changes should be evaluated for dehydration and receive aggressive fluid and electrolyte replacement, if indicated.

A prophylactic treatment is not recommended. As soon as signs of diarrhea occur, the patient should immediately consult his physician and start with the intake of loperamide: 2 capsules (4 mg), thereafter 1 capsule (2 mg) every two hours, for at least 12 hours and for at least 12 hours after the last observation of liquid stool. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use. Sufficient oral rehydration has to be administered during the whole diarrhea episode.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances. In case of persisting severe diarrhea despite loperamide treatment, this drug should be replaced by another antidiarrheic therapy (e.g. octreotide).

4.7.4 Prevention and treatment of neutropenia

Hematopoietic growth factors (i.e., filgrastim or pegfilgrastim) may be used according to institutional or other specific guidelines (e.g. ASCO, EORTC) to treat febrile neutropenia. Due to the high risk of neutropenia together with gastrointestinal toxicity, secondary prophylactic use of G-CSF should be considered after the first chemotherapy associated episode of neutropenia > grade 2, especially in patients >60 years.

Use of any supplementary growth factor must be documented in the patient record. Growth factors must be discontinued at least 48 hours prior to initiation of the next cycle of chemotherapy.

Prophylactic treatment with antibiotics is not allowed.

4.8 EMERGENCY MANAGEMENT

In case of an emergency the coordinating investigator can be approached via the following phone/fax connection:

Prof. Dr. Claus Rödel
Tel.: 069 / 6301-5130
Fax: 069 / 6301-5091
Email : claus.roedel@kgu.de

4.9 PATIENT REGISTRATION AND RANDOMISATION

Subjects fulfilling all in- / exclusion criteria, having provided written informed consent on the approved informed consent form (see appendix), are eligible for participation in the study.

The randomisation is stratified by center and lymph node status (N0 vs. N+), applying an appropriate block randomisation technique.

Enrollment/randomisation is performed centrally at a web-based 24 hour-a-day patient randomization service. Before entering the service the following data must be available:

- Access code
- Center identification
- Name of person performing the randomization
- Month/year of patient's birth
- N status as described above
- further technical details to be defined

The randomisation result (patient no. and treatment allocation) is displayed online immediately.

In case of unavailability, other technical problems, or questions on the randomisation procedure, please contact

WiSP Wissenschaftlicher Service Pharma GmbH
Karl-Benz-Str. 1
40764 Langenfeld
Fax 02173 / 85313 - 11
Tel. 02173 / 85313 - 0

info@wisp.de

by email, fax or phone.

The interval between date of randomization and application of first antineoplastic study medication should not be longer than 14 days.

4.10 PREMATURE WITHDRAWAL OF AN INDIVIDUAL SUBJECT - END OF PROTOCOL SPECIFIED THERAPY

Patients will be removed from protocol-specified treatment for the following reasons:

- disease progression during treatment
- development of unacceptable toxicity
- treatment delay more than 3 weeks
- administration of any other anti-neoplastic medication or any other experimental drug
- investigator decision in the best interest of the patient
- pregnancy or insufficient contraception
- loss to follow-up
- consent withdrawn
- death

The time point of and reason for removal of a patient must be documented on the case report form. The investigator will attempt to complete all discharge procedures at the time a patient is discontinued from study-specific treatment. Further treatment (e.g. surgery) and follow-up data should be recorded, unless the patient withdraws his consent to do so.

Note: If Oxaliplatin only is discontinued, the patient is NOT removed from study-specific treatment.

4.11 PREMATURE STUDY TERMINATION BY THE SPONSOR AND THE COORDINATING INVESTIGATOR

At any time, the sponsor and/or coordinating investigator of the study may terminate the trial participation of an individual patient, as well as the whole trial, provisionally or permanently, if this is required by stringent medical or legal reasons (including insufficient patient recruitment), especially if severe and/or frequent adverse events occur, requiring a new risk/benefit evaluation.

5 TRANSLATIONAL PROGRAM

An extensive translational research program is implemented in order to further refine prognostic and predictive profiling, and eventually identifying subgroups which may be candidates for more intensified preoperative treatment, conservative surgical procedures or even a wait-and-see strategy.

Tumor tissue samples and blood will be collected, processed and stored. Because of the rapid development in the research of biomarkers, the Protocol committee will decide together with the scientific committee of the German Rectal Cancer Group in time about the participation in and/or the generation of a new research program.

6 STUDY ASSESSMENTS AND CRITERIA OF EVALUATION

6.1 OVERVIEW / SCHEDULE OF STUDY ASSESSMENTS

The following two tables give an overview on all study assessment procedures to be performed and documented. It is up to the discretion of the investigator to perform additional or more frequent assessments (e.g. laboratory measurements), generally or individually. However, they do not have to be recorded in the CRF (except for adverse reactions).

Study assessments in treatment arm A

	Screening		Induction chemotherapy					Restaging	Chemoradiotherapy							before surgery[7]	after surgery	4 weeks after surgery close-out	Follow-up[8]
Assessment	**Day -29 to 0**	**Day -7 to 0**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 36-42**	**Day 43**	**Day 50**	**Day 57**	**Day 64**	**Day 71**	**Day 78**	**Day 83**				
Informed consent	X																		
Medical history	X																		
Concomitant diseases/treatment[4]	X		X	X	X	X	X		X	X	X	X	X	X	X				
Physical examination		X	X	X	X	X	X		X	X	X	X	X	X	X	X		X	X
Vital signs		X	X	X	X	X	X		X	X	X	X	X	X	X				
Performance status, weight		X							X			X				X		X	X
ASA physical status classification																X			
Rigid rectosigmoidoscopy	X															X			X[5]
Endoluminal sonography	X[10]																		X[5]
Complete colonoscopic examin.	X																		X[5]
Pelvic MRI	X							X								X			X[5]
CT (thorax, abdomen)[9]	X															X[5]			X[5]
ECG	X							X[5]								X		X[5]	
Hematology[1]		X	X	X	X	X	X		X	X	X	X	X	X	X				
Clinical chemistry[2]		X		X		X			X	X		X	X		X				
Tumormarker CEA		X							X							X		X	X
Surgical findings, pathology																	X		
Symptoms/ toxicity/ adv. events		X		X		X			X	X		X	X		X	X		X[6]	X
Neurolog. assessment	X			X		X			X	X		X	X		X				
Pregnancy test [3]		X																	
Questionnaire life quality		X						X								X			X[11]

1 Hematology: Hb, platelets, WBC, neutrophils
2 Clinical chemistry: sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, LDH, alkaline phosphatase, total protein, albumin
3 Only in fertile women
4 Specified supportive treatment only
5 If clinically indicated
6 Postoperative complications up to 4 weeks after surgery
7 Within one week before surgery
8 Follow-up time schedule according to the guidelines of the Dt. Krebsgesellschaft
9 For exclusion of lung and/or liver metastases only
10 when MRI is not definitive to exclude early cT1/T2 disease in the lower third of the rectum or early cT3a/b tumors in the middle third of the rectum
11 at follow up 6 months, 12 months, then every 12 months

Study assessments in treatment arm B

	Screening		Chemoradiotherapy						Restaging	Pre-operative Chemotherapy						before surgery[7]	after surgery	4 weeks after surgery close-out	Follow-up[8]
Assessment	**Day -29 to 0**	**Day -7 to 0**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 43-56**	**Day 57**	**Day 64**	**Day 71**	**Day 78**	**Day 85**	**Day 92**				
Informed consent	X																		
Medical history	X																		
Concomitant diseases/treatment[4]	X		X	X	X	X	X	X		X	X	X	X	X	X				
Physical examination		X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X
Vital signs		X	X	X	X	X	X	X		X	X	X	X	X	X				
Performance status, weight		X			X					X						X		X	X
ASA physical status classification																X			
Rigid rectosigmoidoscopy	X															X			X[5]
Endoluminal sonography	X[10]																		X[5]
Complete colonoscopic examin.	X																		X[5]
Pelvic MRI	X								X							X			X[5]
CT (thorax, abdomen)[9]	X															X[5]			X[5]
ECG	X								X[5]							X		X[5]	
Hematology[1]		X	X	X	X	X	X	X		X	X	X	X	X	X				
Clinical chemistry[2]		X	X		X	X		X		X		X		X					
Tumormarker CEA		X							X							X		X	X
Surgical findings, pathology																	X		
Symptoms/ toxicity/ adv. events		X	X		X	X		X		X		X		X		X		X[6]	X
Neurolog. assessment	X		X		X	X		X		X		X		X					
Pregnancy test [3]		X																	
Questionnaire life quality		X							X							X			X[11]

1 Hematology: Hb, platelets, WBC, neutrophils
2 Clinical chemistry: sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, LDH, alkaline phosphatase, total protein, albumin
3 Only in fertile women
4 Specified supportive treatment only
5 If clinically indicated
6 Postoperative complications up to 4 weeks after surgery
7 Within one week before/after surgery
8 Follow-up time schedule according to the guidelines of the Dt. Krebsgesellschaft
9 For exclusion of lung and/or liver metastases only
10 when MRI is not definitive to exclude early cT1/T2 disease in the lower third of the rectum or early cT3a/b tumors in the middle third of the rectum
11 at follow up 6 months, 12 months, then every 12 months

6.2 ASSESSMENTS AT RECRUITMENT

The following baseline assessments/procedures will be conducted or obtained within **29 days** prior to start of study treatment:

- Signed written informed consent
- Complete medical history including dates and description of initial diagnosis of rectal cancer, documentation and measurement of all measurable lesions (extension/thickness of the tumor, distance to CRM, infiltration of perirectal fat) and tumor related symptoms
- Relevant concurrent illnesses and relevant concomitant medication.
- Rigid rectosigmoidoscopy with biopsy of the tumor. Measurement of the length of the gross tumor and the distance between the lower tumor margin and anal verge
- High-resolution, thin-sliced (i.e. 3mm) magnetic resonance imaging (MRI) of the pelvis is the mandatory local staging procedure
- Trans-rectal endoscopic ultrasound (EUS) is additionally used when MRI is not definitive to exclude early cT1/T2 disease in the lower third of the rectum or early cT3a/b tumors in the middle third of the rectum
- Spiral-CT of the abdomen and chest to exclude distant metastases
- Complete colonoscopic examination if technically feasible in order to exclude a second colon cancer lesion; if not feasible, a complete colonoscopic examination will be done 6 months after the end of treatment
- Neurological assessment (paresis, paresthesia, brain nerve and reflex status)
- 12 lead ECG

The following baseline assessments will be conducted or obtained within **7 days** prior to start of study treatment unless otherwise indicated:

- Physical examination
- Performance status ECOG (see appendix), weight, height
- Vital signs: blood pressure, pulse rate
- Current symptoms of the underlying tumor disease should be recorded using the NCI Common Toxicity Criteria (see appendix)
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count
- Clinical chemistry: Sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, LDH, alk. phosphatase, total protein, albumin

- Tumormarker CEA
- Urine or serum HCG if patient is of childbearing potential
- Questionnaire life quality: EORTC QLQ-C30, CR38, Wexner-Score

The above tests and procedures are summarized in the Study Flow Sheet.

6.3 ASSESSMENTS DURING AND AFTER STUDY TREATMENT

6.3.1 Assessments during chemotherapy

On the start of chemotherapy day 1 (Arm A) and day 57 (Arm B)

- Performance status
- Weight for (re-)calculation of BSA

Weekly during and one week after chemotherapy

- Physical examination
- Vital signs: blood pressure, pulse rate
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count
- Concomitant diseases/treatment

In addition, on days 15, 29 (Arm A) and 57, 71, 85 (Arm B)

- Neurological assessment
- Toxicity/adverse events according to the NCI Common Toxicity Criteria (see appendix)
- Clinical chemistry: Sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, LDH, alk. phosphatase, total protein, albumin

In addition, within 7 days before or at start of chemoradiotherapy (Arm A) or induction chemotherapy (Arm B):

- Tumor response assessment by pelvic MRI (to exclude early progressive locoregional disease)
- ECG, if clinically indicated
- Questionnaire life quality: EORTC QLQ-C30, CR38, Wexner-Score

6.3.2 Assessments during chemoradiotherapy

On the start of each cycle days 43, 64 (Arm A) and days 1, 22 (Arm B)

- Performance status
- Weight for (re-)calculation of BSA

Weekly during and one week after chemoradiotherapy

- Physical examination
- Vital signs: blood pressure, pulse rate
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count
- Concomitant diseases/treatment

In addition, on days 8, 22, 29, at the end of RT and 1 week thereafter (Arm B) and 43, 50, 64, 71, at the end of RT and 1 week thereafter (Arm A)

- Neurological assessment
- Toxicity/adverse events according to the NCI Common Toxicity Criteria (see appendix)
- Clinical chemistry: Sodium, potassium, calcium, creatinine, urea, bilirubin, GOT, GPT, LDH, alk. phosphatase, total protein, albumin

6.3.3 Assessments before surgery

- Physical examination
- Performance status, weight
- ASA physical status classification system
- ECG
- MRI of the pelvis for tumor response assessment
- Rigid rectosigmoidoscopy for tumor response assessment
- CT thorax, abdomen (if clinically indicated)
- Toxicity/adverse events according to the NCI Common Toxicity Criteria (see appendix)
- Tumormarker CEA
- Questionnaire life quality: EORTC QLQ-C30, CR38, Wexner-Score

6.3.4 Assessments after surgery

- Pathology results (staging, regression grading, resection [R0/1/2]), including translational research (see appendix)

4 weeks after surgery (treatment close-out visit)

- Physical examination
- Performance status, weight
- Tumormarker CEA
- ECG, if clinically indicated
- Toxicity/adverse events according to the NCI Common Toxicity Criteria including postoperative complications

6.3.5 Follow-up procedures

Follow-up examinations take place according to the “Leitlinien der Deutschen Krebsgesellschaft.

The first follow up visit is 6 months after randomization which is approximately 4 weeks after surgery. In case that this two visits overlap, the assessments have to be done only once.

- Physical examination
- Performance status, weight
- Tumormarker CEA
- Clinical tumor assessments, if indicated
- CT of the abdomen and thorax, if indicated
- Endosonography, if indicated
- MRI of the pelvis, if indicated
- Other imaging techniques, if clinically indicated
- Late toxicity/adverse events according to the NCI Common Toxicity Criteria
- Questionnaire life quality: EORTC QLQ-C30, CR38, Wexner-Score at 6 months, 12 months and then every 12 months

6.4 CRITERIA FOR EFFICACY EVALUATION

6.4.1 Clinical/imaging tumor evaluations

Non-pathological measurements of the primary and lymph node lesions are to be made using the same method at each assessment.

All tumor evaluation is performed according to RECIST (Response Evaluation Criteria In Solid Tumors, V. 1.1, 2009) criteria and standards (see appendix).

6.4.2 Pathological tumor evaluations

The pathological examination is performed and documented according to the standards described in appendix. It has to provide data on pCR, regression grading, and R0/1/2 finding including circumferential resection margins (CRM) (distance tumor to CRM).

Complete remission, the primary endpoint, is characterized by ypT0 N0.

In addition, the tumor regression will be scored in 4 grades according the Dworak grade of regression:

0 no regression detectable

1 minimal regression: dominant tumor mass with obvious fibrosis and/or vasculopathy

2 moderate regression: dominantly fibrotic changes with few tumor cells or groups

3 good regression: very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucin pools

4 total regression: no tumor cells detectable microscopically using standard procedures, onlyfibrotic mass or mucin pools

6.4.3 Disease-free survival

Disease-free survival (DFS) is defined as the time interval from **randomization to the first event** of: loco-regional failure after local R0/R1 resection, metastatic recurrence, the appearance of a secondary colorectal cancer or death from any reason.

Patients with

- a tumor that cannot be resected (e.g. due to toxicity)
- macroscopically incomplete local resection (R2 local)
- distant metastases discovered before or at surgery

will also be considered as events. If the patient refuses to be operated by radical surgery due to a clinical complete response (on endoscopy and MRI) and rather opts for a local excision or even a wait and see strategy, this will only be regarded as event in case of local re-growths or distant metastases.

Patients who have not had any such event at the time of data analysis will be censored at the last date they were known to be event-free. Patients with no follow-up records after baseline are not included in the analysis of the secondary time-to-event endpoints.

Patients who have clinical complete response (based on MRI and endoscopy) at pre-surgical re-staging after preoperative treatment are still urgently recommended to undergo radical surgery. If these patients deny to undergo radical surgery, they are closely followed with MRI and endoscopy. Only in case of locoregional regrowth this will be considered as failure.

Diagnosis of recurrence/progression can be made only when the clinical and laboratory findings meet at least one of the criteria defined below:

1. Objective radiological recurrence/progression on radiological imaging (ultrasound, CT scan, MRI scan as indicated by the clinical picture)

2. Positive biopsy (in case of anastomotic recurrence, doubt on radiological imaging or clinically suspected recurrence, e.g. sub-clavicular lymph node or skin metastasis or any palpable mass)

The documented date of recurrence/progression will be the date of confirmation of the recurrence/progression using these methods for diagnosis. At the time of recurrence/progression, the investigator should clearly indicate the site of tumor recurrence/progression and the method of diagnosis. In the absence of obvious radiological evidence of recurrence, positive biopsy must be obtained. An elevated CEA level, as a solitary finding, will not be considered acceptable evidence of rectal cancer recurrence/progression.

6.4.4 Overall survival

All patients will be followed-up for at least 5 years after **randomization** and until death whenever possible.

Overall survival is defined as the time interval between the date of **randomization** and the date of death of any cause. Patients who are still alive when last traced will be censored at the date of last follow-up.

6.4.5 Locoregional failure

Patients will be followed for loco-regional failure irrespective of metastatic recurrence or the appearance of a secondary colon cancer. Loco-regional failure is defined as local or regional recurrence, inoperable locoregional disease, R2 resection. Local recurrence is defined as evidence of tumor in the anastomotic or perineal area. Regional recurrence is defined as evidence of tumor in the pelvic lymph nodes.

6.4.6 Sphincter preservation rate

The inclusion of sphincter preservation as an endpoint raises several problems. Besides the location and the size of the tumor, sphincter preservation depends on surgeon experience and patient condition (degree of continence, length and vascularization of left colon, obesity, narrow pelvis…).

Preoperative treatment will only affect tumor components. It should be noticed at baseline if according to the surgeon the sphincter can be preserved and after the operation if the sphincter has been preserved and if not specified if it was oncologically impossible or oncologically possible but technically not feasible. After undergoing a low anterior resection all margins must be pathologically negative.

Sphincter preservation rate is calculated for the whole patient population in both treatment arms and for the patient group in whom sphincter preservation was feasible according to the baseline decision of the surgeon.

6.5 CRITERIA FOR SAFETY EVALUATION

6.5.1 Toxicity / adverse events (AE)

Adverse events (AE):
An adverse event is defined in the German GCP-V as any untoward medical occurrence in a clinical investigation subject administered an investigaional pharmaceutical product and that does not necessarily have a causal relationship with this treatment.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

The definition of adverse events in this study will include 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 (i.e. 4 weeks after surgery) has been performed or 30 days after the last dose of study treatment (in case of premature withdrawal of an individual subject). SAEs are followed-up until resolved or achieving a stable state.

Adverse drug reactions (ADR):
All untoward and unintended responses to an investigational medicinal product related to any dose should be considered adverse drug reactions (ADR). The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility i.e. the

relationship cannot be ruled out. A serious ADR (SADR) is an ADR that meets the definition of serious (provided below).

Pre-existing diseases, when worsening during study therapy, have to be considered as adverse events. They can lead to serious adverse events, if they meet the criteria described in the section below.

All adverse events and adverse drug reactions are recorded continuously and reported in the AE form of the CRF.

6.5.2 Serious adverse events (SAE) / SUSAR

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- **NOTE:** The term ”life-threatening” in the definition of ”serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect or
- Is an important/significant medical hazard for any other reason

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in cases of important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (eg, emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other important/significant medical hazard” criterion for classification as a serious adverse event.

The definition of serious adverse events in this study will include 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 (i.e. 4 weeks after surgery) has been performed or 30 days after the last dose

of study treatment (in case of premature withdrawal of an individual subject). SAEs are followed-up until resolved or achieving a stable state.

SUSARs (Suspected Unexpected Serious Adverse Reaction) represent Serious Adverse Events related to a study drug (=adverse reactions), considered "unexpected" with regard to the for this study authorized SmPC for the respective chemotherapeutic drug.

Events not to be treated as SAEs:
Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from expedited reporting on a SAE report form (exemptions allowed according to §12, Abs. 4, GCP-V):

- Elective hospitalization and surgery for treatment of the underlying tumor disease
- Elective hospitalization for the performing of protocol-required procedures or administration of study treatment
- Events, including death, that are only and unequivocally caused by progression of the underlying disease
- Any events, occurring after the close out visit (4 weeks after surgery)
- Any events, occurring more than 30 days after the study treatment (in case of premature withdrawal of an individual subject)
- Persistent or significant disability/incapacity, that are unequivocally caused by the underlying disease or known adverse events of therapy (e.g. anastomotic stenosis, incontinence), except they are life-threatening

6.5.3 Methods of recording and assessing adverse events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by subjects are properly captured in the subjects' medical records.

The following **adverse event** attributes must be assigned by the investigator:

- adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known);
- event description (with detail appropriate to the event);
- dates of onset and resolution (and times, in case the event started at the day of study drug administration - if available);
- severity (NCI CTC grade, cf. appendix);
- assessment of relatedness to study treatment;
- action taken;

- outcome.

All AEs must be documented with its maximum NCI CTC severity grade by cycle in the appropriate AE section of the CRF. However, in the CRF, the full set of information is only required for serious adverse events (see below).

For serious adverse events, a SAE report form (initial or follow up) must be completed in addition.

The following detailed information must be recorded for each **serious adverse event** in the CRF:

- A description of the AE in medical terms, not as reported by the subject
- The date of onset (start date)
- The time of onset in case event started at the day of study drug administration - if available (start time)
- The date of recovery (stop date)
- The time of recovery in case event stopped at the day of study drug administration - if available (stop time)
- The grade as assessed by the investigator according to the definitions in NCI-CTC (cf. appendix):
    - Grade 1 = mild
    - Grade 2 = moderate
    - Grade 3 = severe
    - Grade 4 = life-threatening or disabling
    - Grade 5 = death
- The causal relationship to the therapy as assessed by the investigator; the decisive factor in the documentation is the temporal relation between the AE and the study drug. The following judgments of the causality to study drug or study procedures are to be used:
    - Not Related = There is not a temporal relationship to study drug administration (too early, too late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.
    - Not Likely = There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE,
    - Possible = There is a reasonable causal relationship between the study drug and the AE. Dechallenge information (information referring to withdrawal of drug) is lacking or unclear.

- Probable = There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge (withdrawal of study drug). Rechallenge is not required.
- Certain/Definite = There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge and recurs with rechallenge, when clinically feasible.

• Action taken on study drug(s) (none, medication discontinued, dose reduction, medication delayed, reduction of infusion rate).

• Other action (none, concomitant medication given, new or prolonged hospitalization, procedural surgery)

• The outcome according to the following definitions:

- Recovered without sequelae
- Recovered with sequelae
- Ongoing, no therapy of the SAE.
- Ongoing, therapy of the SAE
- Change in toxicity grade/severity
- Died

If in any one subject the same SAE occurs on several occasions, then the SAE in question must be documented and assessed anew each time.

Serious adverse events will be collected and recorded throughout the study period, starting with the first dose of study treatment, ending with the close-out-visit 4 weeks after surgery or, in case of premature withdrawal, 30 days after the last dose of study treatment. Serious adverse events occurring later will NOT be reported unless the investigator feels that the event may have been caused by the study drug or a protocol procedure. However, SAEs will be followed until resolved or considered stable.

6.5.4 Monitoring of subjects with adverse events

Any AE that occurs in the course of the clinical study must be monitored and followed up until the end of treatment visit (i.e. 4 weeks after surgery). It is the responsibility of the investigator that any necessary additional therapeutic measures and follow up procedures are performed.

6.5.5 Procedure for reporting serious adverse events

In the event of the occurrence of any clinical AE or abnormal laboratory test value that is serious (according to the definition provided in section 6.5.2) during the course of the study or the immediate post-treatment period, irrespective of the treatment received by the subject, the investigator is obliged to inform the investigator-sponsor **within 24 hours** by phone or fax to:

WiSP Wissenschaftlicher Service Pharma GmbH
Karl-Benz-Str. 1
40764 Langenfeld
Fax 02173 / 85313 - 11
Tel. 02173 / 85313 - 0
info@wisp.de

The immediate report by the investigator to ***WiSP*** shall be performed using the SAE report form. The immediate and follow up reports shall identify subjects by unique code numbers assigned to the latter. SAEs will be followed until resolved or considered stable.

All SAEs have to be reported on the standard AE form of the CRF as well as on the specific SAE form including all required details.

The subsequent procedures are described in detail in a specifically written operating procedure: ***WiSP*** forwards all SAE reports to the sponsor represented by the study chairman or a person that is designated by the study chairman within one working day. Within one working day, the study chairman or the designated person decides whether the event fulfils the criteria of a SUSAR and informs ***WiSP*** about his decision. ***WiSP*** will ensure that the legal requirements for reporting adverse events to the respective federal agency ("Bundesoberbehörde", BfArM) as well as to the responsible ethical comitee(s), according to §12, Abs. 6 and § 13, Abs. 1 to 7 of GCP-V, are fulfilled.

The sponsor or his delegate are obliged to inform the participating investigators about SUSARs (cf. section 6.5.2 for definition), according to the German regulations (§11, Abs. 2 and 3 of GCP-V).

6.5.6 Pregnancy Reporting

Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 6 months after last study treatment administration must be reported **unhesitatingly** to the CRO. Follow-up information on the subject and her pregnancy outcome should be communicated by the Investigator to the CRO as soon as available.

Please use the pregnancy reporting form for the report and fax the report to:

WiSP Wissenschaftlicher Service Pharma GmbH, **Fax 02173 / 85313 - 11**

The investigator should counsel the subject or the partner of the subject, discuss the risks of continuing the pregnancy, and possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

6.5.7 Overdose

In case of a significant overdose of a study drug, this has to be reported on the serious adverse event form.

7 STATISTICAL ASPECTS

7.1 GENERAL DESIGN

This is an explorative, multi-center, open, randomized phase II study aiming to estimate the efficacy of induction chemotherapy (CT) followed by chemoradiotherapy (CRT), or the other way round, before surgery in patients with locally advanced rectal cancer by comparing exploratively the rates of patients with pathological complete remissions (pCR) between the treatment arms and to expectations derived from historical data.

7.2 SAMPLE SIZE CALCULATION

A total of 304 patients will be randomized to the two treatment arms with a randomization ratio of 1:1 (152 patients per group). Since the primary endpoint pathological complete remission is assessed at surgery, only a small dropout of about 5% is expected, which results in an expected sample size of 144 patients per group. This sample size is sufficient to provide 80% power at an exploratory significance level of 20% (two-sided), assuming that pCR rates for induction CT followed by CRT, or CRT followed by induction CT, respectively, might be improved to about 25% compared to the 15% achieved by the currently standard treatment strategy (cf. references 14 and 16 in section 1.6). Comparing a pCR rate estimated from this trial with a fixed rate of say 15% at a significance level of 10% (one-sided) has a power of 95% assuming a trial pCR rate of 25% given the sample size of 144 patients per group. The power reduces to 87% when the usual two-sided significance level of 5% is used. The sample size gives a probability of 98% (92%) to pick the better treatment regiment for phase III evaluation assuming the pCR rates are 15% (18%) and 25%.

7.3 EVALUATION CATEGORIES OF PATIENTS

All primary analyses will follow the ITT principle, i.e. all eligible patients will be included in the analyses and in the treatment groups they were randomised to. Per protocol (PP) analyses may be carried out as supporting analyses. The analysis populations as well as all other details of the data analyses will be defined in the

Statistical Analysis Plan which will be finalized before final database lock.

7.4 STATISTICAL METHODS

Demographic and clinical baseline characteristics
Summary statistics such as means, standard deviations and quantiles for continuous data and frequencies (proportions) for categorical data will be provided to describe the patients' baseline characteristics such as age, gender, clinical tumor category, clinical nodal category and distance of the tumor from the anal verge.

Efficacy analyses
For the primary efficacy outcome, complete remission (pCR) characterized by ypT0 N0 (see section 6.4.2), the proportions of patients with pCR will be reported with 95% confidence intervals and the treatment groups will be compared in a logistic regression with pCR as dependent variable and treatment and stratification characteristics (center, N status) as factors. The odds ratio describing the treatment effect will be reported with 95% confidence intervals and p-value testing the nullhypothesis of no effect.

Time-to-event data such as recurrence-free survival (see Section 6.4.3) and overall survival (see Section 6.4.4) will be displayed by treatment group as Kaplan-Meyer curves with 95% confidence bands. The treatment effect will be estimated, if appropriate, as a hazard ratio in proportional hazards regression model with treatment and stratification characteristics (center, N status) as factors. The hazard ratio will be reported with 95% confidence interval and p-value testing the null hypothesis of no effect. Dropout will be dealt with as independent right censoring.

Sphincter preservation rate (see Section 6.4.6) is calculated for the whole patient population in both treatment arms and for the patient group in whom sphincter preservation was feasible according to the baseline decision of the surgeon. The analyses will follow the same lines as the pCR analyses described above.

Safety analyses
Adverse events will be summarized by treatment arm, body system and preferred term, intensity, and causal relationship to study agent and their frequencies and percentages will be reported. The safety report is according to ICH E3 "Structure and content of Clinical Study Reports" (CPMP/ICH/137/95).

7.5 ADAPTIVE PROCEDURES / INTERIM AND FINAL ANALYSES

No formal interim analyses are planned. Standard safety follow-up will be conducted by an independent data monitoring committee.

8 STUDY DOCUMENTATION AND ARCHIVING

8.1 DOCUMENTATION AND INFORMATION FLOW

All patient-related data are recorded in a pseudonomized way. Each patient is unequivocally identified by a trial subject number, attributed prior to randomisation into the study. The investigator has to keep a patient identification log, including the full name and address of the subject and eventually additional relevant personal data such as hospital record number, home physician etc. Any patients, including those who were screened in order to be entered into the study, but who could not be recruited for whatever reason (i.e. informed consent not given, not fulfilling selection criteria etc.) are recorded in a "patient screening log".

All the data retrieved during the conduct of the study are entered into the appropriate electronic case record forms (eCRF) by the investigator or another person authorized by the investigator. The access to the eCRFs is provided by WiSP and is explained to the investigator by the study monitor.

All recorded data have to be plausible and complete. Please respect the following technical details when using the CRFs:

- All data fields have to be filled, except for those referring to open questions. If a specific test was not performed or an information item is definitely not available or applicable, information on this should be provided (not done= ND, not applicable = NA, unknown= UK).
- If a value or date is not known exactly, please explain in the comment field.

The investigator is obliged to complete the case report forms within a reasonable time period after retrieval of the data (i.e. usually within 2 weeks). The study office or monitor checks the forms for completeness and plausibility. In case of queries the monitor fills out the query field. The investigator or a delegated person is responsible for clarification/correction/ completion. Queries have to be handled within 4 weeks.

After finalisation of the data checks by the study office/monitor the file or the database is closed.

8.2 DATA ARCHIVING

All relevant study documents including the eCRFs are stored at the office of the coordinating investigator/sponsor for at least 10 years after completion of the final

study report. The investigators have to archive major administrative documents (correspondence with ethical committee, authorities, sponsor etc.), the patient identification log, the signed informed consent forms, and the main study documents (protocol, amendments) for the same time period. The original patient records have to be archived according to the standard procedures of the respective institution, but at least for 10 years.

9 FINANCING

The sponsor will take care of the financing/funding of the study, according to written agreements between the sponsor and the coordinating investigator, the local principal investigators (or their institutions), the contract research organisation (CRO) and the source(s) of funding.

10 USE OF INFORMATION AND PUBLICATION

Any documents supplied in connection with this study, and not previously published, are considered confidential information. This information includes the clinical protocol, workbooks if applicable, case report forms etc. This confidential information, shall not be disclosed to others without prior written consent from the coordinating investigator and shall not be used except in the performance of this study.

The information developed during the conduct of this clinical study is also considered confidential. To allow for the use of the information derived from this clinical study and to insure compliance to current regulations, the investigator is obliged to provide the coordinating investigator with complete test results and all data developed in this study.

The authorship list will be agreed by all investigators prior to publication. The study will only be published once it is completed with respect to the primary endpoint and the corresponding analysis has been performed by the coordinating investigator or his delegate.

11 ETHICAL AND LEGAL REQUIREMENTS

11.1 GENERAL REQUIREMENTS AND AGREEMENTS

The study will be performed according to current legal standards. The ICH E6 Harmonised Tripartite Guideline for Good Clinical Practice, dating from 1997, will be

taken into account. In Germany, the requirements according to the following documents will be fulfilled: Deutsches Arzneimittelgesetz (AMG) "Grundsätze für die ordnungsgemäße Durchführung der klinischen Prüfung von Arzneimitteln" and "Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen“ - all in their current version. The coordinating investigator has at least two years of experience in clinical trials on medicinal products. The Dekan of the University Hospital Frankfurt is the sponsor of the study with respect to GCP regulations (according to article 7 of the EC Commission Directive 2005/28/EC), since the trial at hand is a non-commercial or investigator-initiated clinical trial. The sponsor is responsible for the trial master file according to chapter 4 of the EC Directive 2005/28/EC. The sponsor may delegate this function (or other requirements mentioned in the following sections) to another individual, a company, an institution or an organization.

As the radiation therapy is performed according to current established standards, involvement of the “Bundesamt für Strahlenschutz” (BfS) or reference to the “Atomgesetz” are not required.

11.2 DECLARATION OF HELSINKI

The trial will be performed in accordance with the current version of the Declaration of Helsinki. The declaration is included as appendix.

11.3 INFORMED CONSENT OF THE PATIENT

Before recruitment into the clinical trial each patient will be informed, that participation in the study is completely voluntary, and that he or she may withdraw the participation in the trial at any time without any declaration of reasons. This will not lead to any disadvantage for the respective patient. If the withdrawal is caused by any adverse drug events, the patient should inform the investigator about this fact.

The treating physician will inform the patient about the combined modality treatment to be used and its possible adverse events. At the same time he/she will be informed on the nature and objectives of the study, expected advantages of the participation, possible hazards of the study and alternatives of treatment. The patient will also receive the necessary information on the trial specific insurance and his obligations with this respect. The patient will have sufficient time for his decision and opportunity to ask additional questions. Moreover, the patient will receive a written “patient information” (see appendix), containing all relevant information for the patient's decision and the course of the study.

The consent of the patient to participate must be obtained in writing before recruitment into the study. The informed consent form (see appendix) must be dated

and signed by the patient. Thereby, he declares his voluntary consent to participate in the study and his willingness to comply with the requirements of the trial and the instructions of the treating investigator during the course of the study. **The investigator has to sign the informed consent form after the patient did.** There are two copies of the informed consent form: one for the patient and one to be kept by the investigator in his study documents. The informed consent is only valid after receiving the patient's and the investigator's signature. Thereafter, the patient can be entered into the study if he/she fulfils the selection criteria.

With the declaration of consent the patient agrees that data on his disease are recorded within the framework of the clinical trial and that they are transferred to the sponsor in an pseudonymized way. Moreover, the patient agrees that delegates from the responsible authorities or the sponsor may have direct access to his/her original medical records for trial related monitoring, audit, review and regulatory inspection.

11.4 QUALITY ASSURANCE

11.4.1 Standardisation

The evaluation criteria are similar for all participating centers. Each center has to report its normal ranges for haematology and blood chemistry to the coordinating investigator or his delegate. The respective laboratory institutions have to participate in an appropriate quality assurance program. Toxicity is recorded in a standardized way according to the NCI CTC criteria for categorization and grading.

11.4.2 Monitoring / source data verification

The study will be monitored externally by site visits, written queries and telephone calls to the investigator by personnel that is authorized by the sponsor and the coordinating investigator. Queries or monitoring visits may take place before, during and after recruitment of patients into the study. The number of contacts will depend on the characteristics of the respective center, e.g. the number of recruited patients. According to the investigator's agreement and the patient's informed consent, the monitor is allowed to access the trial documentation and the patients' personal medical records in the participating center.

In order to assure the quality of the data, all entries into the CRFs are formally inspected for completeness and plausibility. During site visits, an additional control with respect to identity of the data recorded in the personal patient records and in the CRF (Source Data Verification) may be performed. The monitor should observe study procedures and will discuss any problems with the investigator.

11.4.3 Audits

In case of an audit by the sponsor or an appropriate authority the investigator will make available all relevant documents. If an audit visit by a regional authority is announced, the respective center should inform the sponsor/coordinating investigator as early as possible in order to allow for an appropriate preparation and support. The inspected investigator or organisational institution of the study will be informed on the result of the audit.

Internal quality reviews will take place at the meetings of the study participants. Therefore the reference board will instruct the participating centers to present their primary documentation of study procedures. The results will be discussed at the meetings to improve the quality of procedures and documentation.

11.5 Registration and request for authorisation of the trial

Prior to start of the trial the sponsor and/or coordinating investigator have to issue a request for authorisation according to § 7, Abs. 1,2,4-6 GCP-V to the "Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM). At the same time he will issue a request for opinion to his competent ethical committee according to § 7, Abs. 1,2,3,5 and 6 GCP-V. In addition, the request for opinion is sent in parallel to the appropriate “local” ethical committees in Germany, formed according to the law of the respective federal states (§ 7, Abs. 1 GCP-V). On behalf of the individual investigators, the sponsor will also announce all individual trial centers to the respective regional authority, according to § 67 of the Arzneimittelgesetz and § 12, Abs. 1 GCP-V.

The respective federal authority will be informed on the course of the study (in parallel to the competent ethical committee, cf. section 9.5), with respect to safety aspects to be announced (according to § 13 GCP-V, Abs. 1-6) as well as with respect to the termination of the trial and its results (according to § 13 GCP-V, Abs. 8 and 9).

11.6 Ethical committee

Prior to start of the trial the study protocol and all other requested documents (cf. section 11.5) will be sent to the competent ethical committee by the sponsor and/or coordinating investigator in order to receive its opinion. The trial is only allowed to start when a positive vote of the ethical committee has been received. During the course of the study the sponsor/ coordinating investigator will inform the ethical committee about all study protocol amendments (cf. section 11.7) as well as all SUSARs from the trial according to § 13, Abs. 2 and 3 GCP-V. In addition, the competent ethical committee will receive a report on all SAEs, and/or a statement on the safety of the study subjects once a year or on request during the course of the

study (according to § 13, Abs. 6 GCP-V). If need be, recommendations of the ethical committee will be included in the study protocol.

In addition, the competent ethical committee will be informed by the sponsor and/or coordinating investigator on the course of the study with respect to the termination of the study and its results (according to § 13, Abs. 8 and 9 GCP-V).

11.7 PROTOCOL AMENDMENTS

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects (cf. § 10, Abs. 1 GCP-V for the decision criteria) will require a formal amendment to the protocol. Such amendment will be agreed upon by the coordinating investigator and the sponsor. It requires a new application to the competent authority and to the competent ethical committee prior to implementation, according to §10, Abs. 2 to 4 GCP-V.

Administrative or technical changes of the protocol such as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, nor on the risk-benefit-ratio, will be agreed upon by the sponsor and the coordinating investigator and will be documented in a memorandum to the protocol. The competent ethical committee may be notified of such changes at the discretion of the sponsor/coordinating investigator.

The sponsor and/or coordinating investigator has to assure, that all amendments have been added to the study documents at any site involved in the trial.

11.8 SUBJECT INSURANCE

An indemnity insurance will be contracted for the trial subjects in accordance with § 40, Abs. 1, Nr.8 and Abs. 3 AMG. The patient will receive all the respective information of relevance to him/her. with

HDI-Gerling Industrie Versicherung AG, Postfach 101027, 40001 Düsseldorf

Versicherungsschein-Nr.: 48 15757572

In order not to jeopardize insurance protection, any health damage occurring in connection with participation in the clinical trial has to be immediately reported by the subject to the insurance company. The patient has to take all appropriate measures to identify the cause and extent of the damage as well as to limit its extent, if possible. Especially he/she is obliged to

- report any adverse event or additional medication to the treating investigator
- consult the treating investigator before applying additional medication or other clinical treatment

11.9 INFORMATION ON STUDY DRUG TO TRIAL INVESTIGATORS

As the chemotherapy drugs administered in this study are routinely used in the medical and combined modality treatment of colorectal cancer for many years, no specific information on this is provided to the investigators. The SmPC of the respective drug is included in appendix.

11.10 DATA SAFETY AND MONITORING BOARD - DSMB

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.

1

12 REFERENCES

1. Roh MS, Colangelo LH, O'Connell MJ, et al: Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 27:5124-30, 2009
2. Sauer R, Becker H, Hohenberger W, et al: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731-40, 2004
3. Rödel C, Sauer R: Integration of novel agents into combined-modality treatment for rectal cancer patients. Strahlenther Onkol 183:227-35, 2007
4. Marquardt F, Rodel F, Capalbo G, et al: Molecular targeted treatment and radiation therapy for rectal cancer. Strahlenther Onkol 185:371-8, 2009
5. Rödel C, Grabenbauer GG, Papadopoulos T, et al: Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer. J Clin Oncol 21:3098-104, 2003
6. Rödel C, Liersch T, Hermann RM, et al: Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer. J Clin Oncol 25:110-7, 2007
7. Rödel C, Arnold D, Hipp M, et al: Phase I-II trial of cetuximab, capecitabine, oxaliplatin, and radiotherapy as preoperative treatment in rectal cancer. Int J Radiat Oncol Biol Phys 70:1081-6, 2008
8. Rödel C, Liersch T, Becker H, et al: Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 13:679-87, 2012
9. Rödel C, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: final results of the German CAO/ARO/AIO-04 randomised phase 3 trial. ASCO 2014, abstract
10. Glynne-Jones R, Counsell N, Quirke P, et al: Chronicle: Results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (Xelox) versus control. Ann Oncol 2014; epub ahead of print.
11. Rutten H, Sebag-Montefiori D, Glynne-Jones R, et al: Capecitabine, oxaliplatin, radiotherapy, and excision (CORE) in patients with MRI-defined locally advanced rectal adenocarcinoma: Results of an international multicenter phase II study. J Clin Oncol 24:153s, 2006 (abstr)
12. Chau I, Allen M, Cunningham D, et al: Neoadjuvant systemic fluorouracil and mitomycin C prior to synchronous chemoradiation is an effective strategy in locally advanced rectal cancer. Br J Cancer 88:1017-24, 2003
13. Chau I, Brown G, Cunningham D, et al: Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol 24:668-74, 2006
14. Chua YJ, Barbachano Y, Cunningham D, et al: Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 11:241-8, 2010
15. Gunnlaugsson A, Anderson H, Fernebro E, et al: Multicentre phase II trial of capecitabine and oxaliplatin in combination with radiotherapy for unresectable colorectal cancer: the CORGI-L Study. Eur J Cancer 45:807-13, 2009
16. Koeberle D, Burkhard R, von Moos R, et al: Phase II study of capecitabine and oxaliplatin given prior to and concurrently with preoperative pelvic radiotherapy in patients with locally advanced rectal cancer. Br J Cancer 98:1204-9, 2008

1

17. Fernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 28:859-65

18. Francois Y, Nemoz CJ, Baulieux J, et al: Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 17:2396, 1999

19. Tulchinsky H, Shmueli E, Figer A, et al: An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 15:2661-7, 2008

20. Kalady MF, de Campos-Lobato LF, Stocchi L, et al: Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. Ann Surg 250:582-9, 2009

21. Garcia-Aguilar J, Smith DD, Avila K, et al: Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 254:97-102, 2011

22. Habr-Gama A, Perez RO, Sabbaga J, et al: Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum 52:1927-34, 2009

23. Glynne-Jones R, Grainger J, Harrison M, et al: Neoadjuvant chemotherapy prior to preoperative chemoradiation or radiation in rectal cancer: should we be more cautious? Br J Cancer 94:363-71, 2006

24. Guerrero Urbano et al: Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. Int J Radiat Oncol Biol Phys 65:907-16, 2006.

25. Roels S. et al., Definition and delineation for the clinical target volume for rectal cancer. Int J Radiat Oncol Biol Phys 65:1129-42, 2006.

26. Nijkamp J, Kusters M, Beets-Tan RG, et al: Three-dimensional analysis of recurrence patterns in rectal cancer: the cranial border in hypofractionated preoperative radiotherapy can be lowered. Int J Radiat Oncol Biol Phys 80:103-10, 2011

27. Gay HA et al. Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas. Int J Radiat Oncol Biol Phys 83(3):e353-62, 2012

28. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery – the clue to pelvic recurrence? Br J Surg 1982;69:613-6.

13 APPENDICES