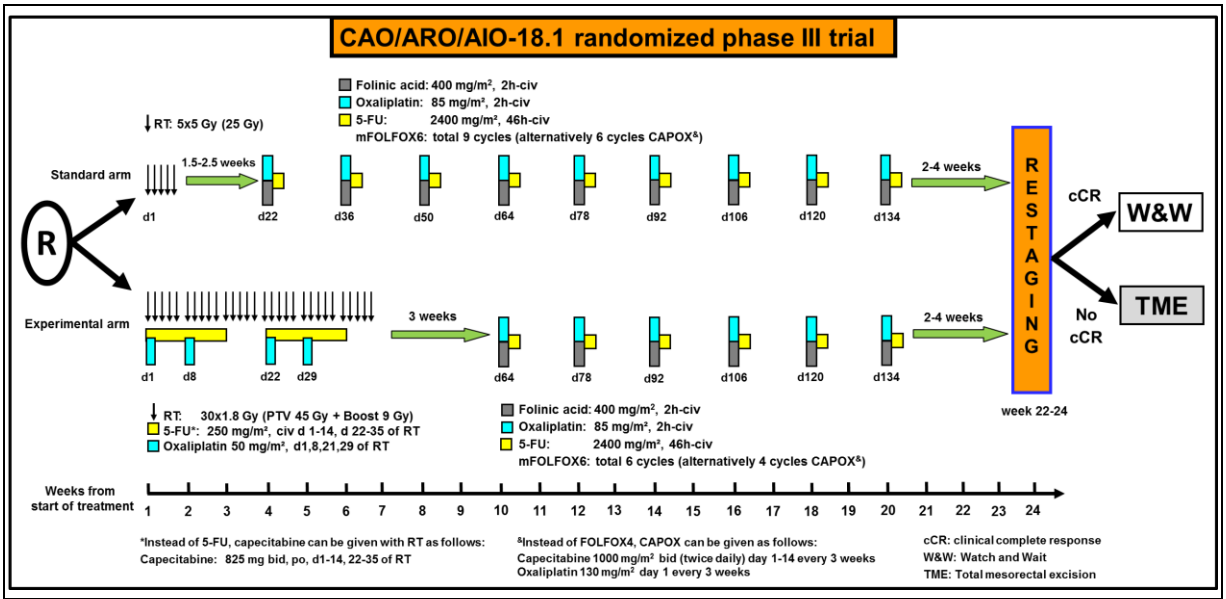
STUDY SYNOPSIS

Title of Study	**Short-course radiotherapy versus chemoradiotherapy, followed by consolidation chemotherapy, and selective organ preservation for MRI-defined intermediate and high-risk rectal cancer patients.**
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
Rationale	Total neoadjuvant treatment (TNT) with either 5x5 Gy followed by FOLFOX/CAPOX consolidation chemotherapy (**RAPIDO**), or induction chemotherapy (mFOLFIRINOX) followed by 5-FU-based chemoradiotherapy (5-FU-CRT) **(PRODIGE 23)** have significantly improved pathological complete response (pCR) and disease-free survival (DFS) compared to preoperative 5-FU-CRT (+/- adjuvant chemotherapy) in recent phase 3 trials for patients with intermediate and/or high-risk rectal cancer. Moreover, randomized phase 2 trials to optimize the sequence of TNT (**CAO/ARO/AIO-12, OPRA**) established CRT followed by consolidation chemotherapy, rather than induction chemotherapy followed by CRT, as the preferred regimen for TNT, based on increased pCR and organ preservation rates, while maintaining excellent compliance, control of distant metastases and DFS. The hereby proposed **ACO/ARO/AIO-18.1** randomized trial aims to directly compare the newly established TNT concepts applying either short-course RT according to RAPIDO, or CRT according to CAO/ARO/AIO-04/-12, both followed by consolidation chemotherapy, and surgery or a watch&wait (W&W) approach for patients with clinical complete response (cCR). The ACO/ARO/AIO-18.1 study incorporates several novel and innovative aspects to further optimize multimodal rectal cancer treatment, partly established by our preceding CAO/ARO/AIO-04 and CAO/ARO/AIO-12 randomized trials: (1) patient selection is based on strict, quality controlled MRI features of intermediate and high-risk characteristics (and, thus, complementary to our ACO/ARO/AIO-18.2 trial in “low-risk” rectal cancer), (2) the CRT regimens incorporates 5-FU/oxaliplatin with doses and intensities shown to be effective and well-tolerated without compromising treatment compliance in CAO/ARO/AIO-04, (3) the sequence of CRT, CT, and surgery/W&W adopts the TNT approach as established by our CAO/ARO/AIO-12 and OPRA trial, (4) surgical stratification allows for W&W management for strictly selected patients with clinical complete response (cCR). Thus,

	we hypothesize that TNT with 5-FU/oxaliplatin-CRT followed by consolidation chemotherapy may increase organ preservation while maintaining DFS as compared to RAPIDO-like short-course RT followed by consolidation chemotherapy.
Study type and study design	Investigator-driven, multicentre, open-labeled, randomized phase III study
Primary objective and endpoint	The primary endpoint of this trial, **organ preservation**, is defined as follows: survival with rectum intact, no major surgery, no stoma. Accordingly, the primary endpoint, organ preservation, will not be reached if any of the following occurs: (1) death, (2) any major surgery other than local excision (R0) performed after randomization, during TNT, at re-staging scheduled 22-24 weeks after start of TNT due to clinical non-complete response, or for any locoregional regrowth after initial clinical complete response requiring salvage-TME, (3) any locoregional regrowth not amenable to salvage surgery, or (4) any stoma (non-re-converted protective stoma within 6 months after completion of TNT, or any stoma needed for toxicity or poor function), whichever occurs first. We hypothesized that the 3-year organ preservation rate will improve from 30% in the control arm to 40% in the investigational arm (hazard ratio of 0.76). With a power of 90% and a two-sided type I error of 5%, the sample size required to obtain a statistically significant difference is 702 patients (564 events) in total.
Secondary objectives and endpoints	• Disease-free survival • Rate of clinical complete response after TNT • Rate of immediate TME after TNT • Cumulative incidence of locoregional regrowth after cCR • Rate of salvage surgery (LE/TME with or without APR/stoma) after locoregional regrowth • Cumulative incidence of local recurrence after (salvage) surgery • Postoperative complications of (salvage) surgery • Rate of sphincter-sparing (salvage) surgery • Pathological TNM-staging • R0 resection rate; negative circumferential resection rate • Tumor regression grading according to Dworak • Neoadjuvant rectal score • Quality of TME according to MERCURY • Acute and late toxicity assessment according to NCI CTCAE V.5.0) • Quality of life and functional outcome based on treatment arm and surgical procedures/organ preservation • Cumulative incidence of distant metastases • 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: • - any cT3 if the distal extent of the tumor is < 6 cm from the anocutaneous line, or • - cT3c/d 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 • - cT3 with clear cN+ based on strict MRI-criteria (see appendix • - cT4 tumors, or • T_{any} middle/low third of rectum with clear MRI criteria for N+ • - mrCRM+ (≤ 1mm), or • - Extramural venous invasion (EMVI+) • 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
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 during treatment and for 6 months after the end of treatment. • 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 • 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 the control arm (see figure below), patients receive 5x5 Gy followed by 9 cycles of consolidation chemotherapy mFOLFOX6 or alternatively 6 cycles of CAPOX, followed by re-staging at week 22-24 as established as new preferred neoadjuvant regimen by the RAPIDO trial. The experimental arm starts with Fluoropyrimidin/Oxaliplatin-based CRT (1.8 Gy to 45 Gy to the primary tumor and pelvic lymph nodes; followed by sequential boost of 9 Gy to the gross tumor volume) followed by consolidation chemotherapy with 6 cycles mFOLFOX6 or alternatively 4 cycles CAPOX, followed by re-staging at week 22-24. In both arms, for patients achieving a clinical complete response (cCR), as strictly assessed by clinical investigation, endoscopy and MRI, a W&W option with close follow-up is scheduled. In case of non-complete response, immediate TME surgery is performed.



Translational research	An extensive translational research program is implemented in order to further refine molecular prognostic and predictive profiling, and eventually identifying subgroups for treatment stratification and conservative surgical procedures.
Sample size and justification	The sample size is driven by the primary efficacy outcome organ preservation. Recruitment will be over 5 years and all patients will be followed up for at least 3 years, unless the patient dies beforehand, resulting in a maximum follow-up of 8 years. For the planning of the study we assume that the event times and times to study withdrawal follow exponential distributions and are independent. Withdrawal from the study is expected to be low; we adjust here for withdrawal of 5% over 3 years. Organ preservation at 3 years is assumed to be 30% in the control arm and increased to 40% in the experimental arm. Hence, a sample size of 351 patients per group yields a power of 90% at a two-sided significance level of 5%. With organ preservation at 3 years of 38.5% in the experimental arm this sample size yields a power of 80%. In total, we aim to randomize 702 patients.
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, organ preservation will be analyzed by Cox proportional hazards regression with treatment and stratification variables of the randomization (center und tumor distance from anal verge, < vs. >= 6cm) as factors. The treatment effect will be reported as hazard ratio with 95% confidence intervals and p-value testing the null hypothesis that the hazard ratio is equal to 1. Patients withdrawing from study treatment will be followed up for the endpoints. Withdrawal from the study will be dealt with as independent right censoring in the primary analysis. If withdrawal from study is substantial and differential between the treatment

	groups, supporting analyses will explore the impact of the independent censoring assumption by use of shared frailty models. The primary endpoint as well as other time-to-event outcomes such as disease-free survival or overall survival will be displayed by treatment group as Kaplan-Meyer curves with 95% confidence bands. The analyses of the time-to-event outcomes among the secondary endpoints will follow the same lines as the analyses of the primary endpoint.
Planned interim analyses	Safety follow-up will be conducted by an independent data safety monitoring committee.
Estimated number of sites	approx. 80 centers of the German Rectal Cancer Study Group
Study duration	Start of preparation: Q2 2018 Start of recruitment: Q3 2020 Planned termination of recruitment: Q3 2025 Planned termination of follow-up: Q1 2029 Final study report: Q2 2029