AIO-KRK-0319: Preoperative FOLFOX versus postoperative risk-adapted chemotherapy in patients with locally advanced rectal cancer and low risk for local failure: A randomized phase III trial of the German Rectal Cancer Study Group (ACO/ARO/AIO-18.2)

AIO-Studie	
Studiennummer/-Code:	AIO-KRK-0319 – ACO/ARO/AIO-18.2
Status:	in Rekrutierung
Rekrutierung:	geplant: ab Q3 2020 bis Q3 2025
Anzahl Patienten:	geplant: 818 randomisiert: 32
Anzahl Zentren:	geplant: 80-100 initiiert: 57 rekrutierend: 55
Weitere Zentren:	Interessierte Zentren wenden sich bitte an: ralf.hofheinz@umm.de
Letzte Aktualisierung	März 2022

Sponsor	University of Heidelberg
Study Chairman (LKP)	Prof. Dr. Ralf-Dieter Hofheinz, Mannheim, for the German Rectal Cancer Study Group (ACO/ARO/AIO)
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Rationale	Patients with locally advanced rectal cancer are generally treated with preoperative 5-FU- or capecitabine-based chemo-radiotherapy (CRT) and total mesorectal excision (TME) surgery in order to decrease the rate of local failure. In patients with low risk for local failure in the middle third of the rectum (cT3a/b, N-) as determined with quality controlled MRI, the German S3 guidelines and the ESMO clinical practice guidelines state that neoadjuvant radiotherapy may be omitted. However, distant failure rate is still substantial in the range of 20-25% in these patients highlighting the need for more effective systemic treatment. The hereby proposed ACO/ARO/AIO-18.2 randomized trial incorporates three novel aspects: (1) patient selection relies on strict and quality controlled MRI features and therefore identifies a cohort without imminent need for radiotherapy, (2) the sequence of chemotherapy and surgery is changed in a way that chemotherapy is administered preoperatively to increase the rate of patients treated with chemotherapy, and (3) three months of neoadjuvant FOLFOX or XELOX (instead of up to 6 months adjuvant chemotherapy) are used as a sole perioperative treatment in order to administer effective doses of the presumably most effective perioperative treatment at an early time point during the course of disease. Thus, patients with locally advanced rectal cancer but low risk for local failure (cT1/2N+ in all thirds of the rectum, cT3a/b N- in the middle third, and cT3-4 Nany in the upper third) will be included and randomized between three months of neoadjuvant FOLFOX/XELOX in Arm A and primary resection of the tumor followed by risk (i.e. stage) adapted chemotherapy in Arm B.
Study type and study design	Investigator-driven, multicenter, open-label, randomized phase III study
Primary endpoint	The primary endpoint of this trial is disease-free survival, defined as the time from randomisation to one of the following events: no surgery or non-radical (R2) surgery of the primary tumour, locoregional recurrence after

	R0/1 resection of the primary tumour, second primary colorectal or other cancer, metastatic disease or progression, or death from any cause, whichever occurred first. We hypothesize that the 3-year DFS probability would improve from 78% in the standard arm to 85% in the investigational arm (hazard ratio of 0.65). With a power of 90% at a two-sided significance level of 5%, the sample size required to obtain a statistically significant difference is 818 patients (233 events) in total.
Secondary endpoints	• Acute and late toxicity assessment according to NCI CTCAE version 5.0 • Compliance (completion rate) of chemotherapy • Surgical morbidity and complications • Pathological UICC-staging, including pCR (ypT0N0) rate • R0 resection rate; negative circumferential resection rate (CRM > 1mm) • Tumor regression grading according to Dworak in the experimental arm • Rate of sphincter-sparing surgery • Rate of W&W with or without local regrowth • Cumulative incidence of local and distant recurrences • Overall survival • Quality of life and functional outcome based on treatment arm, and surgical procedures • Translational / biomarker studies (to be determined)
Inclusion criteria	• Male and female patients with histologically confirmed diagnosis of rectal adenocarcinoma localized 0 – 16 cm from the anal verge as measured by rigid rectoscopy (i.e. lower, middle and upper third of the rectum), depending on MRI-defined inclusion criteria (see below). • Staging requirements: High-resolution, thin-sliced (i.e. 3mm) magnetic resonance imaging (MRI) of the pelvis is the mandatory local staging procedure. • Transrectal endoscopic ultrasound (EUS) is used to help discriminate between T1/2 and early T3 tumors. • MRI-defined inclusion criteria: i. Lower third (0-6 cm): cT1/2 with clear cN+ based on defined MRI criteria, provided CRM- and EMVI- ii. Middle third (≥ 6-12 cm): cT1/2 with clear cN+ provided CRM- and EMVI-; cT3a/b, i.e. evidence of extramural tumor spread into the mesorectal fat of ≤ 5 mm provided N-, CRM-, and EMVI- iii. Upper third (≥ 12-16 cm): cT1/2 with clear cN+ provided CRM- and EMVI-; any cT3-4 irrespective of nodal status. • 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 hematological, hepatic, renal and metabolic function parameters: • Leukocytes ≥ 3.000/mm³, ANC ≥ 1.500/mm³, platelets ≥ 100.000/mm³, 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	• 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 (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 the standard arm B, patients undergo surgical resection of the primary tumor followed by stage- (risk-)adapted adjuvant chemotherapy 4-8 weeks after surgery according to recommendations of the S3 guidelines in analogy to colon cancer. Details of the recommended protocols are provided in the protocol. The experimental arm A starts with 6 cycles of mFOLFOX or 4 cycles of XELOX. Surgery is scheduled four or six weeks after day 1 of the last mFOLFOX or XELOX cycle, respectively. No postoperative chemotherapy is planned.
Translational research	A translational research program, including monitoring by imaging, is implemented in order to further refine 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 disease-free survival. 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. Disease related treatment failure free survival at 3 years is assumed to be of 78% in the control and 85% in the experimental arm, respectively. Hence, a sample size of 409 patients per group yields a power of 90% at a two-sided significance level of 5%. With disease-free survival at 3 years of 84% in the

	experimental arm this sample size yields a power of 80.1%. In total we aim to randomize 818 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 disease-free survival will be analyzed by Cox proportional hazards regression with treatment and stratification variables of the randomization (center und tumor distance from anal verge, i.e. <12 vs. ≥ 12cm) 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 medication 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 recurrence-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.
Interim analyses; data safety monitoring board	No planned interim analyses are foreseen. Safety follow-up will be conducted by a data safety monitoring board (DSMB) on a regular basis which will be defined in a DSMB Charta.
Estimated number of sites	approximately 80-100 centers
Study duration	Start of preparation: Q2 2018 Start of recruitment: Q2 2019 Planned termination of recruitment: Q2 2024 Planned termination of follow-up: Q4 2027 Final study report: Q1 2028