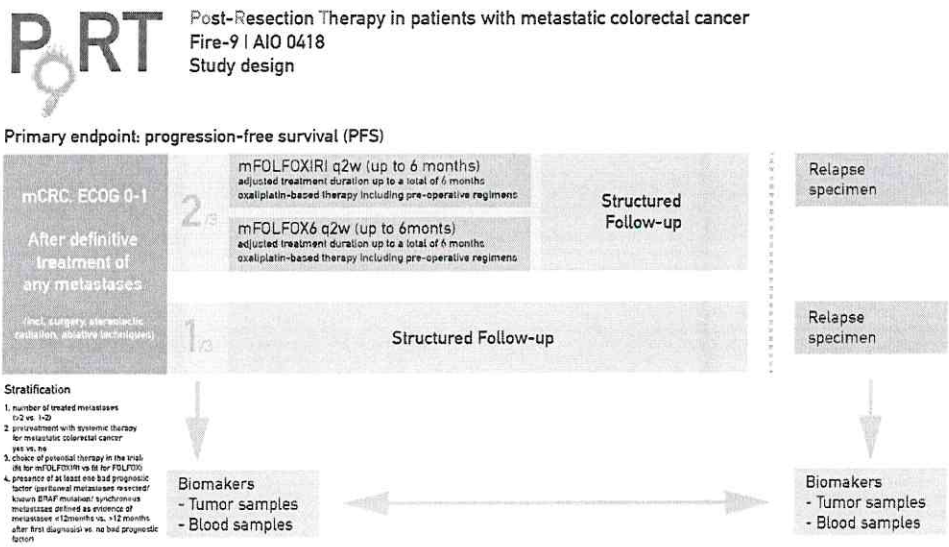
Synopsis

Title	Post-resection/ablation chemotherapy in patients with metastatic colorectal cancer (FIRE-9 - PORT/ AIO KRK0418). Prospective, randomized, open, multicenter Phase III trial to investigate the efficacy of active post-resection/ablation therapy in patients with metastatic colorectal cancer
Short title	mFOLFOXIRI/FOLFOX versus follow-up surveillance after definite treatment of colorectal cancer metastases
Sponsor	Charité Universitätsmedizin Berlin Charitéplatz1 10117 Berlin
Coordinating investigator	Prof. Dr. med. Dominik Modest Charité - Universitätsmedizin Berlin Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie am Campus Virchow Klinikum (CVK) Augustenburger Platz 1 13353 Berlin
Protocol code	FIRE-9 – PORT
AIO trial-no.	AIO KRK 0418
EudraCT no	2020-006144-18
Protocol version and version date	Draft 0.1 of 14-December-2020
Investigational medicinal product(s)	5-FU, folinic acid, irinotecan, oxaliplatin
Clinical trial phase	Phase III
Number of patients	507 patients
Number of trial sites	About 80 trial sites
Indication studied	Post-resection/ablation chemotherapy in patients with metastatic colorectal cancer
Background and rationale	In Germany, colorectal cancer has a prevalence of 65-80/100.000 and a current 5-year mortality of appr. 50% (Robert-Koch-Institut: Krebsdaten 2015; www.krebsdaten.de). In Western Europe, the burden of colorectal cancer is reported to be 211 (female) and 298 (male) diability adjusted life years (DALYs) on a population of 100.000 2. Given the available screening-programs, no severe socioeconomic impact within the incidence appears present. Life-style attitudes however may affect individual risk. Patients with metastases from colorectal cancer (appr. 40-50% of all patients develop metastases) benefit from the resection or ablation of metastates, although relapse occurs in the majority (appr. 70-80%) of these patients 3-7. Clearly, a reduction in relapse rates would improve the long-term outcome of these patients. Unfortunately, additive/adjuvant therapy after local treatment of metastases is not established by phase III trials. Accordingly, no standard of care treatment to improve the relapse rates is available and the current S3-guideline for colorectal cancer does not recommend additive chemotherapy due to insufficient evidence on its benefit (http://www.awmf.org/leitlinien/detail/ll/021-007OL.html), explicitly. The present clinical trial aims to generate evidence that additive therapy after resection or ablation of metastases may improve PFS and OS in patients with colorectal cancer. This is of

	specific importance since both improvements in in localized, but also systemic therapies have resulted in increasing numbers of mCRC patients undergoing resection and/or ablation of metastases4,8-13. Optimal oncological management after removal of metastases is unclear. The result of this trial may be therefore be practice-changing. To support the purely clinical information a supporting translational study will help to identify subgroups (if present) of patients that benefit/ or not from systemic therapy after removal of metastases.
Objectives	**Primary objective** • To compare the efficacy of active additive chemotherapy after definitive treatment of metastases to structured follow-up only **Secondary objectives** • To compare efficacy, safety and patient reported quality of life (QoL) of active treatment to structured follow-up only **Other exploratory objective** Further anti-tumor treatment after discontinuation of study treatment **Translational research objectives** Identification and characterization of patient subgroups with greatest or lowest benefit from treatment including efficacy and toxicity using tumor specimen and blood-based biomarker candidates.
Endpoints	**Primary endpoint** • Progression-free survival (PFS) time at the 24 months follow-up defined as time from randomization to death or evidence of disease as defined by RECIST 1.1 criteria (whatever occurs first) **Secondary endpoints** **Efficacy** • PFS in patients with/without prior systemic therapy • PFS in patients with R1 vs R0 resected lesions as well as ablated vs purely resected lesions • overall survival • safety • treatments (including efficacy) beyond study participation • local control of lesions according to ablative technique (surgery vs. ablation vs. radiation). Local PFS? **Quality of life** • QoL as assessed with the QoL questionnaire EQ-5D-5L **Safety** • Type, incidence, severity, and causal relationship to active chemotherapy of non-serious adverse events and serious adverse events (severity evaluated according to CTCAE version 5.0) **Other exploratory endpoints** Translational analyses including evaluation of tumor specimen of primary and/or metastatic tissue as well as blood samples at different time points • PFS and OS according to circulating tumor DNA at baseline (ctDNA positive vs negative), • outcome in molecular subgroups,

Trial design	This is an open-label, randomized, controlled multicenter phase III study with two parallel arms. Patients with metastatic colorectal cancer after definite interventional therapy of all lesions are randomized in a 2:1 fashion (favoring active therapy) to investigate the efficacy, patient reported quality of life and safety of mFOLOXIRI/FOLFOX as additive treatment versus active follow-up/surveillance. During the randomisation process stratification will be performed according to the following parameters: o number of treated metastases (>2 vs. 1-2) o pretreatment with systemic therapy for metastatic colorectal cancer yes vs. no o choice of potential therapy in the trial: (fit for mFOLFOXIRI vs fit for FOLFOX) o presence of at least one bad prognostic factor (peritoneal metastases resected/ known BRAF mutation/ synchronous metastases defined as evidence of metastases <12months vs 12+months after first diagnosis) vs no bad prognostic factor) Treatment in both arms is continued for a maximum of 12 cycles of 2 weeks interval (i.e. appr. 24 weeks) or until occurrence of progression according to RECIST 1.1 criteria as evaluated by the investigator or unacceptable toxicity. Patients are followed up with regard to survival and if applicable subsequent anti-cancer treatments until death or – after end of study participation – for at least 5 years, whichever date is earlier. The study is displayed in the following figure: 
Inclusion criteria	1. Patient's signed informed consent 2. Patient's age ≥ 18 years at the time of signing the informed consent 3. Histologically confirmed adenocarcinoma of the colon or rectum 4. Resected (R0 or R1) and/or effectively treated metastases (all techniques allowed) of colorectal cancer within 3-10 weeks before randomization AND resected primary tumor (synchronous or metachronous) 5. No radiographic evidence of active metastatic disease at study entry according to RECIST 1.1 in a CT and/or MRI scan not older than 8 weeks. Pre-surgery/ablation images are eligible for the study if all lesions have been addressed.

	6. ECOG performance status 0-2 7. Adequate bone marrow, hepatic and renal organ function, defined by the following laboratory test results: • Absolute neutrophil count ≥ 1.5 x 10^9/L (1500/µL) • Hemoglobin ≥ 80 g/L (8 g/dL) • Platelet count ≥ 100 x10^9/L (75,000/µL) without transfusion • Total serum bilirubin of ≤ 1.5 x upper limit of normal (ULN) • Aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) ≤ 3.0 × ULN • Calculated glomerular filtration rate (GFR) according to Cockcroft –Gault formula or according to MDRD ≥ 50 mL/min or serum creatinine ≤ 1.5 x ULN 8. Patients without anticoagulation need to present with an INR <1.5 x ULN and PTT <1.5 x ULN. 9. Proficient fluorouracil metabolism as defined: a) Prior treatment with 5-FU or capecitabine without unusal toxicity or b) Normal DPYD deficiency test according to the standard of the study centre 10. For females of childbearing potential (FCBP): negative pregnancy test within 14 days before randomisation and agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year during the treatment period and for at least 6 months after the last dose of study treatment. A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male partner's sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. For men: With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for 6 months after the last dose of study treatment. Men must refrain from donating sperm during this same period. With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of study medication to avoid exposing the embryo.
Exclusion criteria	1. Treatment of metastases greater than 3cm with radio-frequency/microwave ablation within 24 months prior to study entry if applicable 2. Treatment of lesions greater than 5cm with radiation (stereotactic/ brachytherapy) within 24 months prior to study entry if applicable 3. Previous chemotherapy for metastatic or localized disease with >6 cycles of FOLFOX (or FOLFOXIRI) or >4 cycles of CAPOX/XELOX 4. New York Heart Association Class III or greater heart failure by clinical judgement 5. Myocardial infarction within 6 months prior to randomisation; percutaneous transluminal coronary angioplasty (PTCA) with or without stenting within 6 months prior to randomization 6. Unstable angina pectoris 7. Unstable cardiac arrhythmia > grade 2 NCI CTCAE despite anti-arrhythmic therapy 8. Ongoing toxicities > grade 2 NCI CTCAE, in particular peripheral neuropathy

	9. Active uncontrolled infection 10. Severe chronic non-healing wounds, ulcerous lesions or untreated bone fracture. 11. Known hypersensitivity to 5-FU, folinic acid, irinotecan or oxaliplatin 12. Major surgical procedure, open biopsy, or significant traumatic injury within 21 days prior to randomisation, or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 21 days prior to randomisation or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure 13. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications. 14. Medical history of other malignant disease than mCRC with the following exceptions: - patients who have been disease-free for at least three years before randomisation - patients with adequately treated and completely resected basal cell or squamous cell skin cancer, in situ cervical, breast or prostate cancer, stage I uterine cancer – patients with any treated or untreated malignant disease that is associated with a 5 year survival prognosis of ≥90% and does not require active therapy 15. Known alcohol or drug abuse 16. Pregnant or breastfeeding females 17. Participation in a clinical trial or experimental drug treatment within 28 days prior to potential inclusion in the clinical trial or within a period of 5 half-lives of the substances administered in a clinical trial or during an experimental drug treatment prior to potential inclusion in the clinical trial, depending on which period is longest, or simultaneous participation in another clinical trial while taking part in this clinical trial. 18. Patient committed to an institution by virtue of an order issued either by the judicial or the administrative authorities 19. Limited legal capacity
Treatment, dosage and administration	**Arm A:** **14-day cycle, choice of (by stratification) intravenous therapy** 1. mFOLFOXIRI: (d1: 2.4g 5-FU in 46 hours, 400mg/qm leucovorin, 85mg/qm oxaliplatin, 150mg/qm irinotecan) 2. mFOLFOX: (d1: 2.4g 5-FU in 46 hours, 400mg/qm leucovorin, 85mg/qm oxaliplatin) ***De-escalations and dose modifications are allowed per institutional standard as investigators decision.*** **Arm A and B:** Radiologic re-assessment with computed tomography is scheduled 3 months (6 cycles of therapy or 3 months observation) and 6 months (12 cycles of therapy or 6 months of observation) after randomisation Structured follow-up for up to 60 months after randomization should be maintained. It is recommended to offer CT scans of thorax/abdomen and/or MRI scans every 3 months within the 2 years after randomisation (6 months =2 controls are part of the study. After the first two relapse-free years, intervals are stretched to 6 months in the third and following years after study participation.

	The treatment is continued in Arm A for a maximum of 12 cycles or until progression according to RECIST 1.1 criteria or unacceptable toxicity whatever comes first.
Translational research	Collection of primary and metastastic tumor tissue and 3 blood sample time points (baseline, 3months, 6 months)
Statistical considerations	The primary endpoint will be PFS (progression-free survival, defined as progression/relapse or death from any cause) at 30 months after randomization. Our assumptions are based on the only available analysis of two pooled, early-stopped trials in the adjuvant/additive setting using fluoropyrimidine monotherapies18 that reported a hazard ratio for PFS in favor of active treatment of 0.76 (the originally reported hazard ratio was reported reversed as 1.32) that translated into a similar effect for the endpoint overall survival. This again support the validity of the primary endpoint PFS in this application. We hypothesize a slightly larger effect for PFS in favor of active therapy due to the 2-3 drug regimens resulting in an estimated hazard ration of 0.70. For the PORT trial18 for the control arm (surgery alone) with structured follow-up, a progression/relapse/death-free rate of 40% at time point 24 months was observed translating into a 60% progression/relapse/death-rate at this time (according to the reported control arm18). With a hazard ratio 0.70 (=□I□□C C=0.0267/0.0382) favoring active treatment, the hypothesized relapse rate at 24 monthsin the intervention arm is assumed to be: 47%. With a power of 80%, a 2-sided alpha of 0,05, a total of 276 events are need to be observed in order to detect a difference in progression-free survival of a hazard ratio of 0.70- favoring active treatment vs. observation (Schoenfeld formula). Assuming an accrual time of 48 months and a follow-up time of 24 months, a drop-out/censoring rate of 40% after 24 months after randomization, a total of 480 patients (320/160 in the respective arms, rounded to receive integers and maintain the allocation ratio) is expected to yield the required number of events if the accrual rate is constant. The computation was done using the software R Version 3.5.1 and the package Rpact. We account for additional 5% of patients that directly leave the study after randomization and never received the study medication. Thus a total of 507 patients (480/507≈0,95) are planned to be recruited.
Duration and end of trial	ca. 4-5 years recruitment and up to 5 years follow-up per patient
GCP statement	The clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the applicable regulatory requirements.