Post-resection/ablation chemotherapy in patients with metastatic colorectal cancer (FIRE-9 - PORT / AIO-KRK-0418)

Prospective, randomized, open, multicenter Phase III trial to investigate the efficacy of active post-resection/ablation therapy in patients with metastatic colorectal cancer

Investigational medicinal products	5-FU, leucovorin, irinotecan, oxaliplatin
EudraCT no.	2020-006144-18
Protocol code	FIRE-9 - PORT
AIO trial-no.	AIO-KRK-0418
Short title	mFOLFOXIRI/mFOLFOX-6 versus follow-up surveillance after definite treatment of colorectal cancer metastases
Sponsor	Charité Universitätsmedizin Berlin Charitéplatz 1 10117 Berlin
Sponsor representative	Prof. Dr. med. Dominik Modest
Version 3.0	28-Sep-2021
Amendment No.	-

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Approval of the Protocol

Trial title: Post-resection/ablation chemotherapy in patients with metastatic colorectal cancer (FIRE-9 – PORT / AIO-KRK-0418)

Prospective, randomized, open, multicenter Phase III trial to investigate the efficacy of active post-resection/ablation therapy in patients with metastatic colorectal cancer

EudraCT no.: 2020-006144-18

I have approved the protocol version 3.0 dated 28-Sep-2021 and confirm that the clinical trial will be conducted in accordance with this protocol, the Declaration of Helsinki, the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements.

I furthermore confirm that the investigators and institutions involved in the clinical trial are to permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents.

Coordinating Investigator and Representative of the Sponsor

Name

Date

Signature

Approval of the Protocol

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Biometrician

Name of the biometrician

Date

Signature

Statement of Compliance

Trial title: Post-resection/ablation chemotherapy in patients with metastatic colorectal cancer (FIRE-9 – PORT / AIO-KRK-0418)

Prospective, randomized, open, multicenter Phase III trial to investigate the efficacy of active post-resection/ablation therapy in patients with metastatic colorectal cancer

EudraCT no.: 2020-006144-18

I have read and understood this protocol and agree to conduct the clinical trial in accordance with this protocol, the Declaration of Helsinki, the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical trial without the prior written consent of the sponsor of the clinical trial.

Principal Investigator

Signature	Date

Principal Investigator

Principal Investigator's Institution

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Abbreviations

5-FU	5-Fluorouracil
ALC	Absolute lymphocyte count
AMG	Arzneimittelgesetz (Medicinal Products Act)
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
β-HCG	beta-Human chorionic gonadotropin
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices
BP	Blood pressure
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CPIC	Clinical Pharmacogenetics Implementation Consortium
CRC	Colorectal Cancer
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTFG	Clinical Trial Facilitation and Coordination Group
DALY	Disability-adjusted life years
DPD	Dihydropyrimidine dehydrogenase
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
e.g.	*exempli gratia* (for example)
EOT	End of Treatment
FFPE	Formalin-fixed, paraffin embedded
FPI	First Patient In
FSH	Follicle-Stimulating Hormone
fT3	free triiodothyronine
fT4	free thyroxine
gamma-GT	Gamma-glutamyltransferase
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung (GCP Ordinance)
GCSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Conference on Harmonization
i.e.	*id est* (that is)
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
i.v.	Intravenous
LDH	Lactate dehydrogenase
LPI	Last Patient In
mCRC	Metastatic Colorectal Cancer
MDRD	Modification of Diet in Renal Disease
mFOLFOX	modified FOLFOX
mFOLFOXIRI	modified FOLFOXIRI
MRI	Magnetic resonance imaging
NCI	National Cancer Institute

OS	Overall survival
P	Pulse
PFS	Progression-free survival
PP	Per protocol
PT	Prothrombin time
PTCA	Percutaneous transluminal coronary angioplasty
QoL	Quality of Life
qxd	every x days
qxw	every x weeks
R0	absence of microscopic residual tumor
R1	presence of microscopic residual tumor
RBC	Red Blood Cell
(S)AE	(Serious) Adverse event
SAP	Statistical Analysis Plan
SmPC	Summary of product characteristics
SOC	Standard of care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Temperature
ULN	Upper limit of normal
UICC	Union for International Cancer Control
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

1 Trial Summary

Title	Post-resection/ablation chemotherapy in patients with metastatic colorectal cancer (FIRE-9 – PORT / AIO-KRK-0418). 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/mFOLFOX-6 versus follow-up surveillance after definite treatment of colorectal cancer metastases
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Coordinating investigator and Representative of the Sponsor	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
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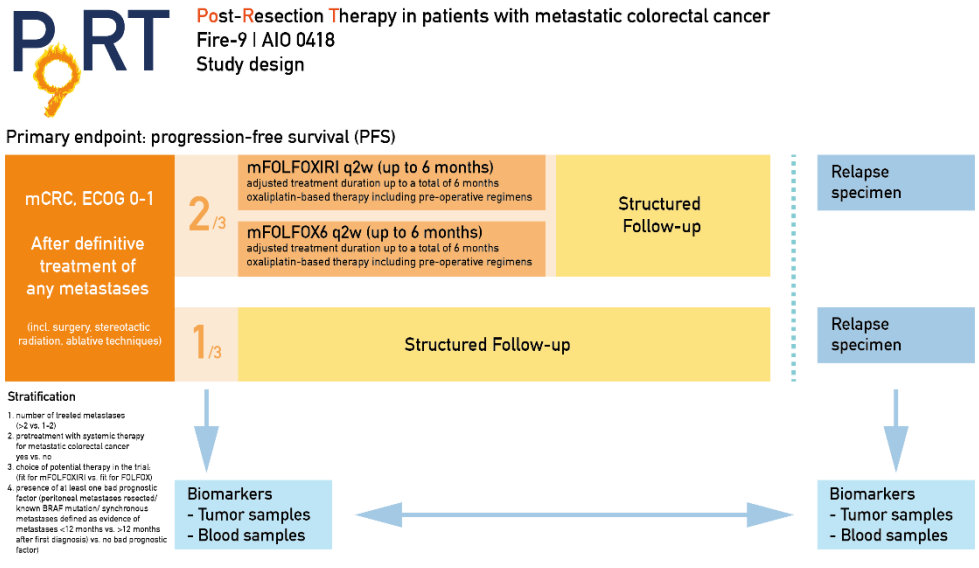
Protocol version and version date	Protocol version 3.0 dated 28-Sep-2021
Investigational medicinal product(s)	5-FU, leucovorin, irinotecan, oxaliplatin
Clinical trial phase	Phase III
Number of patients	To be assessed for eligibility: n ~ 750 To be assigned to the trial, i.e. recruited: n = 507 (338 Arm A/169 Arm B)
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, resulting in a total of ~60.000 new cases every year. Up to 50% of patients develop metastases during the course of their disease while 15-25% already present with synchronous metastases at first diagnosis [Howlader et al., 2011]. The current 5-year mortality is approximately 50% [Robert-Koch-Institut, 2019].In Western Europe, the burden of colorectal cancer is reported to be 211 (female) and 298 (male) disability-adjusted life years (DALYs) on a population of 100.000 [Soerjomataram et al., 2012]. Patients with metastases from colorectal cancer (appr. 40-50% of all patients develop metastases) can benefit from the resection or ablation of metastases, although relapse occurs in the majority (appr. 70-80%) of these patients [Folprecht et al., 2014; Kopetz et al., 2009; Nordlinger et al., 2008; Nordlinger et al., 2013; Van Cutsem et al., 2016]. Clearly, a further 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. The present clinical trial aims to generate the missing 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 localized, but also systemic therapies have resulted in increasing numbers of mCRC patients undergoing resection and/or ablation of metastases [Kopetz et al., 2019; Choti et al., 2016; Cremolini et al., 2015; Cremolini et al., 2017; Heinemann et al., 2014; Luo et al., 2014; Modest et al., 2018].
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 **Further secondary objective** Further anti-tumor treatment **Exploratory objectives** To identify and characterize molecularly-defined patient subgroups and correlate their genetic and molecular tumor characteristics with clinical 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 (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 (OS) • Treatments (including efficacy) beyond study participation • Local control of lesions according to ablative technique (surgery vs. ablation vs. radiation) **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) **Quality of life** • Quality of life (QoL) as assessed with the QoL questionnaire EQ-5D-5L **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 mFOLFOXIRI/mFOLFOX-6 as additive treatment (Arm A) versus active follow-up/surveillance (Arm B). During the randomization process stratification will be performed according to the following parameters: ○ number of treated metastases: i) > 2 vs. 1-2 ○ pretreatment with systemic therapy for metastatic colorectal cancer: ii) yes vs. no ○ choice of potential therapy in the trial: iii) fit for mFOLFOXIRI vs. fit for mFOLFOX-6 ○ presence of at least one of the following unfavorable prognostic factor: iv) peritoneal metastases resected/ known BRAF mutation/ synchronous metastases defined as evidence of metastases < 12 months vs. ≥ 12 months after first diagnosis vs. no unfavorable prognostic factor Treatment in Arm A is continued for a maximum of 12 cycles of 2 weeks interval (i.e. appr. 24 weeks) or until occurrence of progression 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 for at least 5 years after randomization, whichever date is earlier. The trial design 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. Absence of significant active wound healing complications (if applicable) prior to randomization. Resolved wound healing complications after resection/ablation are acceptable for inclusion into the trial. 6. No radiographic evidence of active metastatic disease at study entry 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 in the interval. 7. ECOG performance status 0-2. 8. 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 (100000/µL) without transfusion • Total serum bilirubin of ≤ 1.5 x upper limit of normal (ULN) • Aspartate aminotransferase (AST/GOT) ≤ 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 9. Patients without anticoagulation need to present with an INR < 1.5 x ULN and PTT < 1.5 x ULN. Patient with prophylactic or therapeutic anticoagulation are allowed into the trial. 10. Proficient fluorouracil metabolism as defined: a) Prior treatment with 5-FU or capecitabine without unusal toxicity or b) If tested, normal DPD deficiency test according to the standard of the study site or c) If tested, in patients with DPD deficiency test with a CPIC activity score of 1.0-1.5 fluoropyrimidine dosage should be reduced by 50% 11. For women of childbearing potential (WOCBP): negative pregnancy test within 14 days before randomization 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 3 cm with radio-frequency/microwave ablation within 24 months prior to study entry if applicable. 2. Treatment of metastases greater than 5 cm 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 randomization; 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 by investigator's perspective. 10. Severe chronic non-healing wounds, ulcerous lesions or untreated bone fracture. 11. Known hypersensitivity to 5-FU, leucovorin, irinotecan or oxaliplatin or to any of the other excipients listed in section 6.1 of the corresponding SmPC. 12. Bone marrow depression after radio- or chemotherapy. 13. Severe kidney dysfunction (creatinine clearance < 30 ml/min) or changes in blood count. 14. Recent or concomitant treatment with brivudine. 15. Peripheral sensitive neuropathy with functional impairment (> grade 1 acc. to CTCAE version 5.0 (see appendix)). 16. Inflammatory bowel disease and/or bowel obstruction. 17. Simultaneous application of Johannis herbs preparations. 18. Pernicious or other megaloblastic anaemia caused by vitamin B12 deficiency. 19. If tested, DPD deficiency test with a CPIC activity score <1. 20. Major surgical procedure, open biopsy, or significant traumatic injury within 21 days prior to randomization, or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 21 days prior to randomization or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure. 21. 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. 22. Medical history of malignant disease other than mCRC with the following exceptions: - patients who have been disease-free for at least three years before randomization

	- 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 23. Known alcohol or drug abuse. 24. Pregnant or breastfeeding females. 25. 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. 26. Patients depended on Sponsor, investigator or study site. 27. Suspected SARS-CoV-2 infection with or without symptoms (evaluation according to local policy in respective center with respect to actual status of pandemic and with reference to the policy that would apply to patients with similar therapy outside the trial). This may include assessment of vaccination status, anamnesis, physical examination and potentially antigen and/or PCR testing. 28. Patient committed to an institution by virtue of an order issued either by the judicial or the administrative authorities. 29. Limited legal capacity.
Treatment, dosage and administration	**Arm A:** **14-day cycle (q14d), choice of (by stratification) intravenous therapy for up to 12 cycles*:** mFOLFOXIRI: Oxaliplatin 85 mg/m^2 2h day 1, Irinotecan 150 mg/m^2 90min day 1, Leucovorin 400 mg/m^2 1-2h day 1, followed by 5-FU 2400 mg/m^2 46h. or mFOLFOX-6: Oxaliplatin 85 mg/m^2 2h day 1, Leucovorin 400 mg/m^2 1-2h day 1, 5-FU 400 mg/m^2 bolus**, followed by 5-FU 2400 mg/m^2 46h. **NOTE: Both regimens should be adjusted individually for the total dose of oxaliplatin, i.e. a maximum of 12 cycles taking neoadjuvant therapy any other treatment prior to the planed trial intervention into account. Thus, for patients pre-treated with q14d FOLFOX(IRI) or q21d CAPOX/XELOX, the trial intervention should be adjusted by a de-escalation to FOLFIRI or further to fluoropyrimidine monotherapy (following FOLFOXIRI) or to single-agent fluoropyrimidine (following FOLFOX) to allow for a total trial intervention duration of 6 months (see Section 5.2.3.1 for details).* ***5-FU 400 mg/m^2 bolus can be used according to site specific routine.* ***Further de-escalations and dose modifications are allowed per institutional standard as investigators decision.*** The treatment is continued in Arm A for a maximum of 12 cycles or until relapse/progression according to the local investigator or unacceptable toxicity whatever comes first.

	Arm A and B: Within the structured follow-up for up to 60 months after randomization CT scans of thorax/abdomen and/or MRI scans should be scheduled every 3 months within the 24 months after randomization. After the first two relapse-free years, intervals are extended to 6 months in the third and following years after randomization.
Translational research	The translational research program consists of the following steps but might be modified or expanded taking latest scientific data into account: 1. Characterization of the initial resected/ablated tumor (primary and/or metastases) for DNA mutations and RNA expressions (for example panel NGS and mRNA expression analysis) 2. Longitudinal assessments of tumor markers and circulating tumor DNA (according to initial tumor characteristics), assessments should include the baseline, 3 months and 6 months timepoints (and further timepoints as long as no relapse occurred). 3. Characterization of tumor specimen obtained after relapse of disease during or after study (if occurring and available) for DNA mutations and RNA expressions. 4. Correlation of 1) with 3) and eventually also correlation of relapse tumor tissue with acquired changes in samples of 2) This paired sample collection including relapse specimen plus the longitudinal assessment of circulating tumor DNA will be performed in order to inform about early detection of relapse (potentially prior to radiographic correlate), relapse patterns (based on initial spread and the ablative technique) and molecular background of relapse (tumor evolution, secondary mutations, expressions).
Statistical considerations	The primary endpoint will be PFS (progression-free survival, defined as progression/relapse or death from any cause) at 24 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 monotherapies [Mitry et al., 2008] 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 trial. 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 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 arm [Mitry et al., 2008]). With a hazard ratio 0.70 ($=\lambda_I/\lambda_C$ C=0.0267/0.0382) favoring active treatment, the hypothesized relapse rate at 24 months in 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 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.

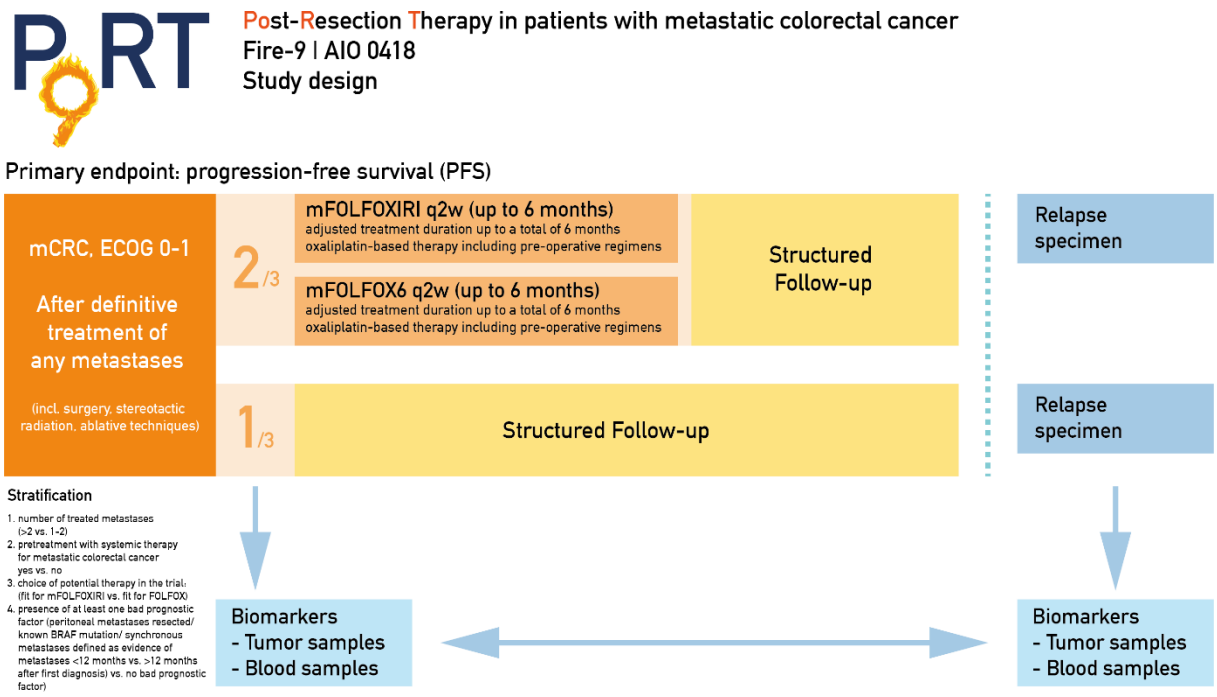
Duration and end of trial	**Recruitment** First patient in (FPI) to Last patient in (LPI): 48 months **Analysis** Primary endpoint (PFS) at 24 months after randomization: LPI + 24 months (72 months total) Secondary endpoints: LPI + 60 months (108 months total) **End of Study (EOS)** Last visit of last patient (LVLP) Last patient in (LPI) + 60 months (FPI + 108 months in total)
GCP statement	This 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.

2 Trial Design

2.1 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 mFOLFOXIRI/mFOLFOX-6 as additive treatment (Arm A) versus active follow-up/surveillance (Arm B).

Figure 1: Illustration of Trial Design



2.2 Trial Scheme

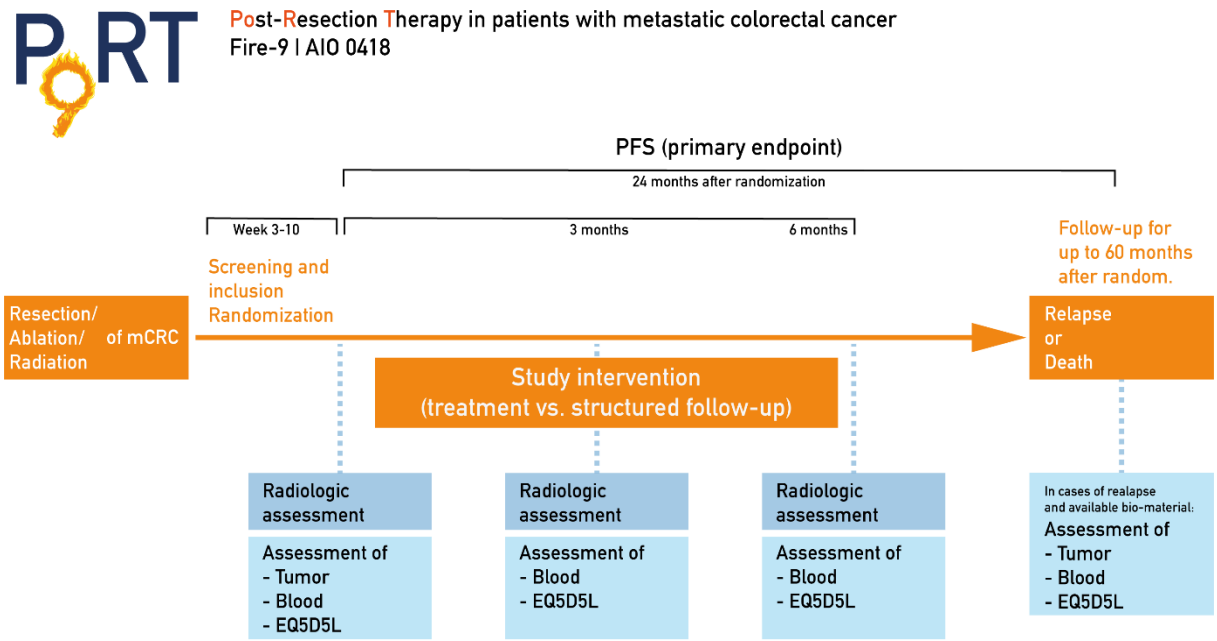
The trial will consist of both a clinical and translational part. During the study, re-assessments (radiologic assessment, blood and QoL) will be conducted for all trial subject of the trial every 3 months. Tumor biopsies will be collected at screening (baseline sample) and in case of relapse of disease if a new tumor sample is obtained.

The objective of the re-assessments is detection of relapse either radiologically or within the translational material (blood samples with ctDNA dynamics and tumor – if available from relapses). CT scans of thorax/abdomen and/or MRI scans will be performed every 3 months within the 2 years after randomization. After the first two relapse-free years, intervals should be stretched to 6 months in the third and following years after study start. Structured follow-up for up to 60 months after randomization should be maintained for both arms.

Patients in Arm A receive additive study drug intervention (mFOLFOXIRI or mFOLFOX-6) for up to six months (12 cycles) after randomization with additional clinical and safety assessments as specified in Section 2.3.

Allocation to study treatment FOLFOX/FOLFOXIRI for patients in Arm A is stratified and done by investigator's choice. The decision considers but is not limited to factors as age, performance status, previous therapy, and side effects of previous therapy. Since obligatory criteria cannot be made treatment allocation will not be regulated by the protocol but stratification will avoid that treatment allocation promotes any bias.

Figure 2: Study Flow Chart



2.3 Schedule of Trial Activities

Table 1: Schedule of Activities

Trial Period:	**Pre-study SOC intervention[#]**	**Screening and Randomization Phase**	**Structured Follow-up (Arm A and B)**			
			+ Trial Intervention (Arm A only)			
Timing and assessment window:	up to 10 weeks prior to random.	Inclusion is possible 3-10 weeks after the SOC intervention after successful screening	3mo. (± 2w)	6mo. (± 2w)	9mo. - 24mo. (q3mo. ± 2w)[§]	at least 60mo. after random. or until death (q6mo. ± 1mo.)
Administrative Procedures						
Definite treatment of colorectal cancer metastases	**A/B**					
Informed Consent		**A/B**				
Inclusion/Exclusion Criteria		**A/B**				
Demographics and Medical History		**A/B**				
Prior and Concomitant Medication Review[a)]		**A/B**	**A**			
Prior FOLFOX(IRI) or CAPOX/XELOX therapy		**A/B**				
Randomization		**A/B**				
Clinical Procedures/Assessments						
ECOG Performance Status		**A/B**	**A/B**	**A/B**	**A/B**	
Full Physical Examination[b)]		**A/B**			**A‡**	
Directed Physical Examination			**A**	**(A)**		
Review Adverse Events[c)]		**A/B**	**A/B**		**A/B**	
Height[d)], Weight and Vital Signs (T, P, BP)		**A/B**	**A**	**(A)**	**A‡**	
12-Lead Electrocardiogram[e)]		**A/B**	**A**	**A**	**A‡**	
Covid-19 assessment[r)]		**A/B**	**A**	**A**	**A**	

Trial Period:	**Pre-study SOC intervention#**	**Screening and Randomization Phase**	**Structured Follow-up (Arm A and B)** + **Trial Intervention (Arm A only)**													
Timing and assessment window:	up to 10 weeks prior to random.	Inclusion is possible 3-10 weeks after the SOC intervention after successful screening	3mo. (± 2w)						6mo. (± 2w)						9mo. - 24mo. (q3mo. ± 2w)§	at least 60mo. after random. or until death (q6mo. ± 1mo.)
mFOLFOXIRI or mFOLFOX-6 or de-escalated treatment regimens, if applicable (q14d + 5d)[f]			**A**	**A**	**A**	**A**	**A**	**A**	**A**	**A**	**A**	**A**	**A**	**A**		
Further anticancer therapy status			**A/B**													
Survival Status			**A/B**						**A/B**						**A/B**	**A/B**
Laboratory Procedures/Assessments																
Pregnancy Test – Urine or Serum β-HCG[g]		**A/B**	**A**		**A**		**A**		**A**		**A**		**A**	**A‡**		
PT/INR and aPTT[h]		**A/B**	**(A)**													
CBC with Differential[i],[j]		**A/B**	**A**	**(A)**										**A‡**		
Comprehensive Serum Chemistry Panel[i],[k]		**A/B**	**A**	**(A)**										**A‡**		
Quality of Life																
EQ5D5L Questionnaire		**A/B**	**A/B**						**A/B**						**A/B**	**A/B**
Efficacy Measurements																
Tumor Imaging and CEA	A/B	**A/B[l]**	**A/B[m]**						**A/B[m]**						**A/B[m]**	**A/B[n]**
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																
Archival or Newly Obtained Tissue Collection / Biopsy		**A/B[o]**	**A/B[p]**													
Correlative Biomarker Studies / Blood Collection[q]		**A/B**	**A/B**						**A/B**						**A/B**	

Pre-study treatment of colorectal cancer metastases by ablation/radiation should be performed to study site specific routine and is considered SOC.

§ If the patient progresses within 24 months after randomization an additional visit (=EOT visit) should be scheduled as timely as possible and the corresponding assessment should be performed.

‡ The regular assessments should be performed during the last chemotherapy cycle. If the patient progresses earlier an additional visit (=EOT visit) should be scheduled as timely as possible and the corresponding clinical and laboratory assessments should be performed.

A/B To be conducted/assessed/measured for both Arms.

A To be conducted/assessed/measured for Arm A.

(A) To be conducted/assessed/measured for Arm A according to study site standards or if clinically indicated; only to be documented if abnormal.

a) Prior and concomitant medication should be reviewed for both Arms to assess eligibility. For Arm A, concomitant medication should also be reviewed during chemotherapy.

b) Full physical examination at Screening and after last dose of trial intervention. Directed physical examination during treatment cycles as per study site standards or if clinically indicated. It is recommended to interview patients during the COVID-19 pandemic for respective symptoms including fever, cough and headaches and to initiate comprehensive diagnostic in cases of suspected infections. It is also recommended to assess patients during the COVID-19 pandemic according to the individual policy as regulated by the site, county or state.

c) Adverse events should be reviewed for both Arms to assess eligibility. For Arm A, adverse events should be documented during trial intervention at every visit and up to 4 weeks after the last chemotherapy administration. For Arm B, adverse events should be queried at every visit (planned and unplanned) during the first 7 months from randomization – but at least twice – by an unbiased open question. Thereafter, adverse events should be queried every three months for both groups by an unbiased open question for up to two years after randomization.

d) Height will be measured at Screening only. Vital signs should include temperature, pulse and blood pressure.

e) To be repeated prior to the first administration if ECG from screening is older than 8 weeks. To be performed at least once during treatment, i.e. at cycle 7.

f) mFOLFOXIRI regimen: Oxaliplatin 85 mg/m² 2h day 1, Irinotecan 150 mg/m² 90min day 1, Leucovorin 400 mg/m² 1-2h day 1, followed by 5-FU 2400 mg/m² 46h.

mFOLFOX-6 regimen: Oxaliplatin 85 mg/m² 2h day 1, Leucovorin 400 mg/m² 1-2h day 1, followed by 5-FU 2400 mg/m² 46h. A 5-FU bolus of 400mg/m² prior to the 5-FU continuous infusion might be administered at the discretion of the investigator.

See protocol section 5.2 for dose adjustments in patients with a reduced DPD activity.

See protocol section 5.2.3.1 for de-escalated treatment regimens in case of previous oxaliplatin application.

g) To be performed in women of childbearing potential only. WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test. This test should be repeated a maximum of 24 hours before study drug administration. Following initiation of treatment, pregnancy testing will be performed every second cycle (at least monthly) during treatment and until the end of relevant systemic exposure to the study medication in accordance with the CTFG guidance on contraception.

h) Quick's time [PT/INR], aPTT. Quick's time [PT/INR] during treatment is clinically indicated – and therefore needs to be monitored – in case of concomitant use of 5-FU and oral anticoagulants.

i) These assessments may be performed up to 3 days prior to the treatment administration in order to have the results available on the visit day.

j) White Blood Cell (WBC) count with differential & Absolute Neutrophil Count (ANC); Absolute Lymphocyte Count (ALC); Red Blood Cells (RBCs); Platelet count; Hemoglobin; Hematocrit.

k) Alkaline phosphatase; Aspartate aminotransferase (AST); Potassium; Sodium; Total Bilirubin; Direct Bilirubin (If total bilirubin is elevated above the upper limit of normal); Creatinine.

l) Separate tumor imaging at Screening will only be performed if last available tumor imaging is older than 10 weeks. Carcinoembryonic antigen (CEA) should be determined in addition.

m) Tumor imaging during the first 24 months after randomization will be performed every 3 months (q3mo. ± 2 weeks) calculated from the date of the last imaging. Earlier imaging can be performed if clinically indicated. CEA should be determined in addition to monitor the efficacy of therapy.

n) Tumor imaging thereafter will be performed every 6 months (q6mo. ± 1 mo.) calculated from the date of the last imaging. Earlier imaging can be performed if clinically indicated. CEA should be determined in addition to monitor the efficacy of therapy.

o) If patients consent to accompanying translational research project: Archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue (archived specimen ≤ 6 months may be acceptable).

p) If patients consent to accompanying translational research project: If the patient progresses and a new biopsy is obtained within the clinical routine.

q) If patients consent to accompanying translational research project: EDTA blood (10 ml), serum (10 ml) and Streck tubes (10 ml) samples should be taken at Screening and every three months during the first 24 months after randomization and every 6 months thereafter. For patients in Arm A, the blood samples for the 3 months and 6 months timepoint should be drawn prior to the study medication administration (pre-dose).

r) Assessment of Covid-19 should be conducted according to the actual pandemic situation AND institutional policy that is applied to any patients that receives FOLFOX/FOLFOXIRI for colorectal cancer outside the trial. This may require assessment of vaccination status, physical examination, anamnesis and Covid-19 tests (e.g. antigen test and/or PCR testing). SARS-CoV-2-positive patients should not participate in the trial or chemotherapy application should be delayed as long as the patient is positive for SARS-CoV-2.

3 Objectives(s), Hypothesis(es), and Enpoint(s)

3.1 Primary Objective, Hypothesis, and Endpoint

(1) **Objective:**
To compare the efficacy of active additive chemotherapy after definitive treatment of metastases to structured follow-up.

Hypothesis:
Active additive chemotherapy after definitive treatment of metastases improves progression-free survival.

Corresponding Endpoint:
PFS – Progression-free survival time defined as time from randomization to death or evidence of disease relapse/progression (whatever occurs first)

3.2 Secondary Objective(s), Hypothesis(es), and Endpoint(s)

(1) **Objective:**
To compare efficacy of active treatment to structured follow-up by further efficacy parameters and in different subgroups.

Hypothesis:
Subgroups, defined by various clinical parameters, display differences in efficacy after active additive chemotherapy after definitive treatment of metastases.

Corresponding Endpoint(s):
PFS in

- patients with/without prior systemic therapy;
- in patients with R1 vs. R0 resected lesions;
- patients with ablated vs. purely resected lesions.

OS – Overall survival (OS) as time from randomization to the date of death of any cause.

Number and type of treatments (including efficacy) beyond study participation.

Local or distant control of lesions according to ablative technique (surgery vs. ablation vs. radiation)

(2) **Objective:**
To compare safety of active treatment to structured follow-up only

Hypothesis:
Number of patients with SAEs is higher in the active treatment arm compared to the structured follow-up, but comparable to fluoropyrimidine regimes in similar settings.

Corresponding Endpoint:
(Serious) Adverse Events – 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)

(3) **Objective:**
To compare patient reported quality of life (QoL) of active treatment to structured follow-up only.

Hypothesis:
QoL is moderately impacted by the active treatment for patients in Arm A, but comparable to fluoropyrimidine regimes in similar adjuvant settings.

Corresponding Endpoint:
QoL – Quality of life (QoL) as assessed with the QoL questionnaire EQ-5D-5L.

3.3 Exploratory Objective

(1) **Objective:**
To identify and characterize patient subgroups with greatest benefit from treatment including efficacy and toxicity using tumor specimen of primary and/or metastatic tissue as well as blood samples at different time points for the identification of biomarker candidates

Hypothesis:
Molecularly-defined subgroups display differences in efficacy and safety after active additive chemotherapy after definitive treatment of metastases.

Corresponding Endpoint:
PFS, OS and Safety according to circulating tumor DNA at baseline (ctDNA positive vs. negative).

PFS, OS and Safety according to molecular subgroups.

4 Background and Rationale

4.1 Colorectal Cancer Incidence

Colorectal cancer (CRC) is one of the most frequent malignancies in developed countries and one of the leading causes of cancer-related deaths [Ferlay et al., 2007; Garcia et al., 2007; Siegel et al., 2012]. Worldwide there are more than 1 million new cases diagnosed every year.

In Germany, colorectal cancer has a prevalence of 65-80/100.000, resulting in a total of ~60.000 new cases every year. Up to 50% of patients develop metastases during the course of their disease while 15-25% already present with synchronous metastases at first diagnosis [Howlader et al., 2011]. The current 5-year mortality is approximately 50% [Robert-Koch-Institut, 2019].

In Western Europe, the burden of colorectal cancer is reported to be 211 (female) and 298 (male) disability-adjusted life years (DALYs) on a population of 100.000 [Soerjomataram et al., 2012]. Given the available screening-programs in developed countries, no severe socioeconomic impact within the incidence appears present. Life-style attitudes however may affect individual risk.

4.2 Treatment Options for Colorectal Cancer

When diagnosed before nodal involvement, treatment is usually limited to surgical resection. Patients with nodal involvement are candidates for adjuvant chemotherapy with fluoropyrimidines with or without oxaliplatin following initial surgery in the attempt to prevent metastatic recurrence of the disease [Schmoll et al., 2012]. Once spread to distant sites, treatment essentially consists of palliative chemotherapy.

4.2.1 Fluoropyrimidine plus Oxaliplatin Regimes in Metastatic Colorectal Cancer

For most patients with metastatic colorectal cancer (mCRC) palliative chemotherapy regimens with fluoropyrimidines and oxaliplatin and/or irinotecan remain the standard of care in first- and second-line therapy [Van Cutsem et al., 2016].

A randomized phase III trial conducted by the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) demonstrated a comparable efficacy in case of overall response rate (ORR), progression free survival (PFS) or overall survival (OS) between an irinotecan-based (FOLFIRI; irinotecan, leucovorin and 5-fluorouracil (5-FU)) or an oxaliplatin-based first line chemotherapy (mFOLFOX-6; oxaliplatin, FA and 5-FU [Tournigand et al., 2004]).

However, differences were observed in case of side effects and toxicity with higher numbers of patients suffering from grade 3 or 4 mucositis and nausea/vomiting treated with FOLFIRI and higher numbers of patients developing grade 3 and 4 neutropenia and neurosensory toxicity treated with mFOLFOX-6.

After failure of first line therapy, irinotecan- or oxaliplatin-based 5-FU-containing chemotherapeutic regimes have also been shown to improve OS in second line therapy of patients with mCRC [Andre et al., 1999a; Andre et al., 1999b; de Gramont et al., 1997;

Maindrault-Goebel et al., 1999; Maindrault-Goebel et al., 2000; Maindrault-Goebel et al., 2001].

4.2.2 Further Treatment Options for Metastatic Colorectal Cancer

Patients with metastases from colorectal cancer (appr. 40-50% of all patients develop metastases) can benefit from the resection or ablation of metastases, although relapse still occurs in the majority (appr. 70-80%) of these patients [Folprecht et al., 2014; Kopetz et al., 2009; Nordlinger et al., 2008; Nordlinger et al., 2013].

Consequently, interventional treatment (surgery, ablation, radiation) with intent to definitely treat one or several metastases has been integrated into the treatment algorithm of metastatic colorectal cancer and is therefore recommended in current guidelines [Van Cutsem et al., 2016].

The evolution of these strategies and consecutive recommendations mostly focus on therapy of liver metastases due to the high frequency of this localization (75-80% of all patients) [Van Cutsem et al., 2016]. Nevertheless, other metastatic lesions are also treated accordingly if the course of disease allows for it (i.e. lung, peritoneum, bone, etc.) [Van Cutsem et al., 2016; Carpizo et al., 2009; Gonzalez et al., 2013; Patel et al., 2016].

4.3 Rationale

The treatment of metastases has become an increasingly frequent situation due to the advancements made in surgical and other interventional techniques (such as ablation, brachytherapy, stereotactic radiation and others). However, whether patients benefit from further additive/adjuvant therapy remains elusive, since the benefit of 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 unlike the previous editions, the current S3-guideline for colorectal cancer does not recommend additive chemotherapy since 2017 due to insufficient evidence on its benefit (http://www.awmf.org/leitlinien/detail/ll/021-007OL.html). This recommendation however is not reflected by other guidelines like the ESMO guideline [Van Cutsem et al., 2016]

The present clinical trial aims to generate the missing 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 localized, but also systemic therapies have resulted in increasing numbers of mCRC patients undergoing resection and/or ablation of metastases [Kopetz et al., 2009; Choti et al., 2016; Cremolini et al., 2015; Cremolini et al., 2017; Heinemann et al., 2014; Luo et al., 2014; Modest et al., 2018].

4.3.1 Rationale for FOLFOX or FOLFOXIRI as post-resection/ablation therapy

Studies investigating peri- or postoperative therapy in the context of surgery of metastases have addressed more or less homogeneous cohorts of liver-limited disease with low risk profile for relapse from an actual perspective [Nordlinger et al., 2008; Nordlinger et al., 2013; Mitry et

al., 2008; Primrose et al., 2014]. Unfortunately, these studies have failed to define a standard for systemic therapy in the context of intervention (i.e. surgery) in metastatic disease.

Several aspects have limited the implementation: one study represents a pooled analysis of two trials with a fluoropyrimidine application (bolus 5-FU) that is no longer used and has been replaced by more effective and less toxic regimens (oral capecitabine or infusional 5-FU) [Mitry et al., 2008]. Moreover, the effect on outcome was of borderline-significance due to the reduced size of the respective trials.

The second major trial in metastatic colorectal cancer investigated pre- and postoperative therapy with a combination regimen (FOLFOX) vs. operation of liver metastases alone. Importantly, the median number of metastases resected in this trial was “1”- clearly comprising a cohort with favourable risk which due to evolution of therapy is not directly comparable to patients with resected metastases in the context of current treatment algorithms. The study described a trend towards improvement in outcome that did not translate into a clear benefit in survival [Nordlinger et al., 2008; Nordlinger et al., 2013].

The rationale for using FOLFOX or FOLFOXIRI as post-resection/ablation treatment is based on the fact that these regimens are standard of care in many first- and second-line therapies and have proved to be efficacious in various settings, i.e. neoadjuvant, adjuvant and palliative.

Dosage of the here applied mFOLFOXIRI is mainly based on the adjuvant pancreas study from Conroy et al., 2018, which also applied 2400mg/m² of 5-FU and 150mg/m² of Irinotecan. Although it is not the same entity, the extrapolation of the therapeutic situation (preceded, often complex surgery of the upper gastrointestinal tract) seems to be an important factor for the safety and tolerability of this regimen.

mFOLFOX-6 is a standard regimen for adjuvant therapy of colorectal cancer. The use of a 5-FU bolus is optional to address eventual pre-existing toxicities.

4.3.2 Rationale for Study Design and Endpoints

Since there is no established standard and no evidence of clinical improvement by systemic treatment after treatment of metastases from colorectal cancer, the control arm will offer structured oncological observation every 3 months to patients, which is also recommended as standard of care in the actual German treatment guidelines [Schmiegel et al., 2017]. As intervention – knowing that many patients will present with subclinical metastases, a highly active triplet-regimen (mFOLFOXIRI) or a standard adjuvant regimen (mFOLFOX-6), developed both in palliative and adjuvant treatment settings of gastrointestinal cancer will be offered to patients [Andre et al., 2004; Conroy et al., 2011; Conroy et al., 2018; Grothey et al., 2018; Loupakis et al., 2014]

Progression-free survival (PFS) is the primary endpoint of this trial defined as time from randomization to progression (new metastases) or death from any cause. PFS is an established surrogate endpoint in trials promoting adjuvant or additive therapy and correlates with overall survival (i.e. time form randomization to death from any cause) [Saad et al., 2010 and references therein].

Secondary endpoints include PFS in patients with/without prior systemic therapy, in patients with R1 vs. R0 resected lesions as well as ablated vs. purely resected lesions. Further

secondary endpoints are overall survival, safety, quality of life, number and type of treatments (including efficacy) beyond study participation, PFS and OS according to circulating tumor DNA at baseline (ctDNA positive vs. negative), outcome in molecular subgroups, local control of lesions according to ablative technique (surgery vs. ablation vs. radiation). These endpoints and subgroup analyses are foreseen to identify those patient populations who benefit most/least from a post-resection/ablation therapy to allow for a potential fine-tuning of treatment in the future.

As part of the translational research project, blood samples are collected as part of the structured follow-up to create a collection of patient material with and without relapse. Moreover, the relapses will be recorded as part of the study protocol, including the collection of additional tumor tissue and blood samples, if possible, at the time of relapse. Understanding the genetic and molecular tumor characteristics, their longitudinal changes and correlating this with the baseline characteristics (prior systemic therapy, ablative technique used, resection status) and clinical outcome will provided the most complete set of data to answer whether patients – and if so, which patients – benefit from an additive/adjuvant therapy after local treatment of metastases.

In summary, the optimal oncological management after removal of metastases is still unclear and results of this trial may therefore be practice-changing.

4.4 Ethical Considerations and Benefit-Risk Assessment

Patients with treated metastases from colorectal cancer represent a high-risk cohort for development of new metastases and consecutively death. Therefore, intervention with systemic therapy appears clearly justified, also taking into account that intervention with a combination regimen (fluoropyrimidine plus oxaliplatin) is accepted in patients with lower stage (UICC III) of disease and less risk of relapse. The intervention – although not recommended by the actual German guidelines and supported by data – is often discussed in tumor boards, regularly leading to “individual” solutions without data that justify chemotherapy in these patients – which is also in accordance with European perspectives (ESMO). Participating patients will therefore receive either standard of care on the basis of available evidence (watch and wait-observation including structured follow-up), or as intervention, up to 6 months of therapy that was so far not evaluated in this clinical setting that invokes subclinical metastases in the majority of patients at the time of study start. Therefore, a potential disadvantage, although possible, seems unlikely. The study will therefore either provide a basis for routine treatment of patients or alternatively confirm that additive treatment does not provide a relevant benefit and should not be promoted. These observations will be made in the context of a quality of life assessment. The trial will be conducted according to the declaration of Helsinki, German laws and with respect to protection of data privacy.

5 Methodology

5.1 Trial Population

Investigators will recruit patients directly during regular clinical consultation visits in the respective center, e.g. after being discussed in a multidisciplinary tumor board. All study related investigations and enrolment of patients will only be performed after a written consent was collected using the ethics committee approved patient information and consent forms (refer to protocol section 10.4).

Patients fulfilling the inclusion-/exclusion criteria (see below) will be captured online in the eCRF as screening patients to obtain a patient number which is used for pseudonymized identification throughout the study.

5.1.1 Inclusion Criteria

Participants are eligible to be included in the trial only if all of the following criteria apply:

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. Absence of significant active wound healing complications (if applicable) prior to randomization. Resolved wound healing complications after resection/ablation are acceptable for inclusion into the trial.
6. No radiographic evidence of active metastatic disease at study entry 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 in the interval.
7. ECOG performance status 0-2.
8. Adequate bone marrow, hepatic and renal organ function, defined by the following laboratory test results:
   - Absolute neutrophil count $\geq$ 1.5 x 10^9/L (1500/µL)
   - Hemoglobin ≥ 80 g/L (8 g/dL)
   - Platelet count ≥ 100 x10^9/L (100000/µL) without transfusion
   - Total serum bilirubin of ≤ 1.5 x upper limit of normal (ULN)
   - Aspartate aminotransferase (AST/GOT) ≤ 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
9. Patients without anticoagulation need to present with an INR < 1.5 x ULN and PTT < 1.5 x ULN. Patient with prophylactic or therapeutic anticoagulation are allowed into the trial.

10. Proficient fluorouracil metabolism as defined:
    a) Prior treatment with 5-FU or capecitabine without unusal toxicity

       or

    b) If tested, normal DPD deficiency test according to the standard of the study site

       or

    c) If tested, in patients with DPD deficiency test with a CPIC activity score of 1.0-1.5 fluoropyrimidine dosage should be reduced by 50%
11. For women of childbearing potential (WOCBP): negative pregnancy test within 14 days before randomization 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.

5.1.2 Exclusion Criteria

Participants are excluded from this trial if any of the following criteria apply:

1. Treatment of metastases greater than 3 cm with radio-frequency/microwave ablation within 24 months prior to study entry if applicable.
2. Treatment of metastases greater than 5 cm 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 randomization; 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 by investigator's perspective.
10. Severe chronic non-healing wounds, ulcerous lesions or untreated bone fracture.
11. Known hypersensitivity to 5-FU, leucovorin, irinotecan or oxaliplatin or to any of the other excipients listed in section 6.1 of the corresponding SmPC.
12. Bone marrow depression after radio- or chemotherapy.
13. Severe kidney dysfunction (creatinine clearance < 30 ml/min) or changes in blood count.
14. Recent or concomitant treatment with brivudine.
15. Peripheral sensitive neuropathy with functional impairment (> grade 1 acc. to CTCAE version 5.0 (see appendix)).
16. Inflammatory bowel disease and/or bowel obstruction.
17. Simultaneous application of Johannis herbs preparations.
18. Pernicious or other megaloblastic anemia caused by vitamin B12 deficiency.
19. If tested, DPD deficiency test with a CPIC activity score <1.
20. Major surgical procedure, open biopsy, or significant traumatic injury within 21 days prior to randomization, or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 21 days prior to randomization or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure.
21. 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.
22. Medical history of malignant disease other than mCRC with the following exceptions:
    - patients who have been disease-free for at least three years before randomization
    - 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
23. Known alcohol or drug abuse.
24. Pregnant or breastfeeding females.
25. 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.
26. Patients depending on Sponsor, investigator or study site.
27. Suspected SARS-CoV-2 infection with or without symptoms (evaluation according to local policy in respective center with respect to actual status of pandemic and with reference to

the policy that would apply to patients with similar therapy outside the trial). This may include assessment of vaccination status, anamnesis, physical examination and potentially antigen and/or PCR testing.

28. Patient committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
29. Limited legal capacity.

5.1.3 Lifestyle Considerations

5.1.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.1.3.2 Contraception

FOLFOX and FOLFOXIRI-based chemotherapy may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant during trial intervention, the participant will be immediately discontinued from trial intervention(s). The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor or designee if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or new-born). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or new-born to the Sponsor or designee. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor or designee and followed as described in Section 6.2.2.5.

5.2 Trial Intervention(s)

The study drug intervention(s) to be used in Arm A of this trial are mFOLFOX-6 or mFOLFOXIRI. A guidance is outlined in Table 2, however, at the discretion of the investigator, site specific modifications are permitted, e.g. additional 5-FU bolus, parallel leucovorin and oxaliplatin administration or variation of the infusion rates.

Table 2: Trial Medication (guidance for administration)

Drug	Dose/Potency	Duration of administration***	Route of Administration	Day(s) of application
mFOLFOX-6 regimen:				
Oxaliplatin **Leucovorin** **5-FU***	85 mg/m² 400 mg/m² 400 mg/m² bolus** 2400 mg/m²	2h 1-2h 2-5 min 46h	IV Infusion IV Infusion IV Infusion IV Infusion	d1 of each chemotherapy cycle
mFOLFOXIRI regimen:				
Oxaliplatin **Irinotecan** **Leucovorin** **5-FU***	85 mg/m² 150 mg/m² 400 mg/m² 2400 mg/m²	2h 90min 1-2h 46h	IV Infusion IV Infusion IV Infusion IV Infusion	d1 of each chemotherapy cycle

* in DPD mutation carriers with a CPIC activity score of 1.0-1.5, 5-FU Dosage should be reduced by 50%.
** additional 400mg/m² bolus is permitted but not mandatory.
*** infusion rates of chemotherapeutical components represent recommendations but might be modified according to local standards

The guidance given in this protocol section does not replace the careful reading of the summary of product characteristics (SmPC) for each component!

5.2.1 Timing of Dose Administration

Trial interventions should be administered on day 1 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Trial Activities (Section 2.3). From the second cycle onwards, the chemotherapy may be administered up to 5 days after the scheduled day 1 of the respective cycles, due to administrative reasons with a minimum time span of 14 days between the cycles.

All trial interventions will be administered on an outpatient basis.

5.2.2 Prerequisites for Application of Trial Intervention

The following rule must be followed, as it describes an exclusion criterion:

- The patient is not eligible to participate in this study if
  - > 12 weeks (> 6 cycles) of FOLFOXIRI or FOLFOX (q14d cycles)

    or
  - > 12 weeks (> 4 cycles) of CAPOX or XELOX (q21d cycles)

    or
  - a combination of the above therapies accumulating in > 12 weeks of therapy

  was received as pre-treatment.

5.2.3 Treatment Modification and Toxicity Management of FOLFOX/FOLFOXIRI Chemotherapy

5.2.3.1 De-escalation

It is strongly recommended that both regimens are adjusted individually for the total dose of oxaliplatin taking neoadjuvant/adjuvant therapy any other pre-treatment prior to the planed trial intervention into account in order to achieve up to 12 cycles of trial intervention.

NOTE: In the below guidance, early terminated cycles will be counted as full cycle.

- It is recommended to de-escalate the patient's trial intervention from mFOLFOXIRI to FOLFOX or FOLFIRI or further to fluoropyrimidine monotherapy or from mFOLFOX-6 to a single-agent fluoropyrimidine regimen, respectively according to the following rules:
    - For each q14d cycle of FOLFOXIRI or FOLFOX pre-treatment the oxaliplatin is omitted for the same number of cycles during trial intervention; e.g. 3 cycles of FOLFOX pre-treatment results in the omission of oxaliplatin in cycle 10-12 of trial intervention.
    - Each q21d CAPOX or XELOX cycle in pre-treatment counts 1.5-fold. Thus, the number of CAPOX or XELOX cycles is to be multiplied by 1.5 and rounded up. The oxaliplatin is omitted for the same number of cycles during trial intervention; e.g. 3 cycles of CAPOX count as 4.5 pre-treatment cycles to be rounded up to 5. Thus, oxaliplatin is omitted in cycles 8-12 of trial intervention.
    - For a combination of the above therapies, each cycle of FOLFOXIRI or FOLFOX pre-treatment counts as 1 cycle and each cycle of CAPOX or XELOX pre-treatment counts as 1.5 cycles. The cycle numbers are added and rounded up. Oxaliplatin is omitted from the same number of cycles of trial intervention.
    - In case of irinotecan-related toxicity in FOLFOXIRI treated patients de-escalation to FOLFOX and further to fluoropyrimidine monotherapy is possible.

5.2.3.2 Dose Modification

Hematologic Toxicity:

In case of neutrophil granulocytes < 500/µl and/or thrombocytes < 50000/µl at any time during the treatment cycle, therapy should be stopped until the prerequisites for starting a new cycle are met. The anticancer components considered related to the adverse event should be reduced by 25% of the starting dose in the following cycle, the 5-FU bolus should be omitted if applicable. Alternatively, GCSF application can be considered in case of neutropenia at the discretion of the Investigator and is recommended in patients receiving mFOLFOXIRI. A maximum of two dose reductions (total reduction of 50% in comparison to the initial dose) is allowed in every chemotherapeutical agent.

However, at the discretion of the Investigator, a chemotherapeutical agent can be interrupted or omitted without having previously used the dose reductions suggested below. Chemotherapy can be continued with drugs not being related to the observed toxicity.

Febrile neutropenia: Chemotherapy should be held. GCSF administration should be considered. The dosage of all components should be reduced by 25%, the 5-FU bolus should be omitted if applicable.

Non-hematologic toxicity:

The following table (Table 3) gives an overview on dose adjustments of the chemotherapeutic agent most likely responsible for the observed toxicity.

Table 3: Chemotherapy Dose Adjustments in case of chemotherapy associated toxicity

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to Grade 0-1 then continue at same dose with prophylaxis where possible (alternatively continue at 75% of the original dose).	Interrupt treatment until resolved to Grade 0-1, then continue at 75% of original dose with prophylaxis where possible.	Discontinue treatment unless investigator considers it to be in the best interest of the patient to continue at 50% of original dose, once toxicity has resolved to Grade 0-1. (after approval by the Sponsor)
2nd appearance of the same toxicity	Interrupt treatment until resolved to Grade 0-1, then continue at 75% of original dose.	Interrupt treatment until resolved to Grade 0-1, then continue at 50% of original dose.	
3rd appearance of the same toxicity	Interrupt treatment until resolved to Grade 0-1, then continue at 50% of original dose.	Discontinue treatment permanently	
4th appearance of the same toxicity	Discontinue treatment permanently		

5.3 Methods against Bias

Given that the control (Arm B) is “watch and wait-observation”, no placebo should be applied, also to prevent from the potential benefit of the observational group for not being at the hospital, not needing an intravenous port system etc.

5.3.1 Minimizing Selection Bias

5.3.1.1 Treatment Allocation

Screened and eligible patients will be included in the trial after initiation of the study. Patients will be allocated in a strictly concealed way by 2:1 randomization (Intervention vs. Control) block with variable block lengths randomization.

5.3.1.2 Stratification

During the randomization process stratification will be performed according to the following binary stratification variables:

- number of treated metastases:
  - i) > 2 vs. 1-2
- pretreatment with systemic therapy for metastatic colorectal cancer:
  - ii) yes vs. no
- choice of potential therapy in the trial:
  - iii) fit for mFOLFOXIRI vs. fit for mFOLFOX-6
- presence of at least one of the following unfavorable prognostic factor:
  - iv) peritoneal metastases resected/ known BRAF mutation/ synchronous metastases defined as evidence of metastases < 12 months vs. ≥ 12 months after first diagnosis vs. no unfavorable prognostic factor

5.3.2 Minimizing measurement bias

Due to the nature of the intervention, blinding is not possible. However, given that the intervention in this trial is well established chemotherapy regimen, a center-driven bias caused by differing expertise appears highly unlikely and will not be compensated for.

5.4 Concomitant Medication

5.4.1 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All relevant concomitant medication will be recorded on the electronic case report form (eCRF).

All relevant concomitant medications received within 28 days before the first dose of study treatment until the last administration of study drug should be recorded. If participants experience an SAE, concomitant medication administered 4 weeks after the last administration of study drug are to be recorded as defined in Section 6.2.

Covid-19 vaccination is explicitly permitted and recommended if necessary, at any time during the course of the study, all available vaccines are allowed. It is at the investigator's discretion to delay chemotherapy after vaccination.

5.4.1.1 Supportive Care

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

5.4.2 Prohibited Concomitant Medications

Patients in Arm A should not receive any of the following medications during the active treatment phase:

Any concurrent (investigational or non-investigational) other anti-tumor therapy such as cytotoxic chemotherapy, hormonal therapy, biological therapy (including monoclonal antibodies) or immunotherapy. Any other medication that should not be combined with any of the used drugs within the trial as listed in the corresponding SmPCs.

5.5 Removal from Study Treatment and Withdrawal from Study

Patients will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/removed if necessary, to protect their health (see reasons for withdrawal below). It is understood that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Patients that will be withdrawn from the study will not be replaced.

Patients must be removed from study treatment for the following reasons:

- Toxicities requiring discontinuation in the meaning of persistent study drug related grade IV SAEs according to the current SmPCs not treatable by de-escalation or discontinuation of the causing agent e.g. thrombocytopenia (< 100.000/mm³), leukocytopenia (< 3.500/mm³), mouth ulcer, stomatitis, diarrhea, bleeding, hemorrhage after 5-FU application or anaphylactic reaction, intestinal ischemia, sepsis, neutropenic sepsis, septic shock, macroangiopathic hemolytic anemia, disseminated intravascular coagulation, QT prolongation, rhabdomyolysis, gastrointestinal ulcer after Oxaliplatin application.
- Withdrawal of consent
- Relapse/progression of disease
- Death
- Investigator decision (in the best interest of the patient)
- Lost to follow up
- Non-compliance
- Pregnancy or insufficient contraception
- Termination of the study by the Sponsor

If a SARS-CoV-2 infection occurs during treatment phase, antineoplastic treatment must be suspended for the time of active infection.

If there is a medical reason for withdrawal of treatment, the patient will remain under the supervision of the investigator until the AEs have been resolved or declined to baseline values. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the eCRF. In case

of discontinuation of the study treatment, the investigations scheduled for the EOT visit should be performed.

If a patient withdraws consent for further study treatment during the treatment phase, the patient should still be followed for structured follow-up (i.e. documentation of the 3-monthly visits). If a patient withdraws consent for further participation in the study, follow-up assessments will be discontinued.

Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

In any case, the eCRF section entitled "End of Study" must be completed.

5.6 Study Discontinuation

The whole study may be discontinued at the discretion of the Sponsor in the event of any of the following:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Occurrence of AEs unknown to date in respect of their nature, severity and duration or the unexpected incidence of known AE

Further the study will be discontinued if:

- Favorable opinion and/or approval is revoked
- A necessary adaption of the maximum insurance sum in not possible

6 Trial Procedures and Assessments

6.1 Trial Procedures

- Study procedures and their timing are summarized in the Schedule of Trial Activities in Section 2.3. Individual trial procedures are described in detail below.
- Adherence to the trial design requirements, including those specified in the Schedule of Trial Activities in Section 2.3 is essential and required for trial conduct. Nevertheless, it may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training and experience) staff.
- All screening evaluations must be completed and reviewed to confirm that potential trial participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Additional evaluations/testing may be deemed necessary by the Investigator or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g. HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Trial Activities (Section 2.3).

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in the clinical trial and before any study related procedures are performed. If there are changes to a participant's status during the study (e.g. health requirements) the investigator must ensure appropriate consent is in place.

6.1.1.2 General Informed Consent

Consent must be documented by the participant's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/IEC's

approval/favourable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about the trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

6.1.1.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria (Section 5.1.1 and Section 5.1.2) will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for this trial.

6.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the patient's colorectal cancer for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.5 Prior and Concomitant Medications Review

6.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Prior anti-cancer treatment, if allowed by the inclusion/exclusion criteria, for the patient's colorectal cancer will be recorded separately and not listed as a prior medication.

6.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record relevant medication, if any, taken by the participant during the trial. All medications related to reportable SAEs should be recorded as defined in Section 6.2.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Schedule of Activities (Section 2.3) and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix 2: Common Terminology Criteria for Adverse Events V5.0 (CTCAE). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading and action taken with regard to study intervention.

Please refer to Section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Full Physical Exam

The Investigator or qualified designee will perform a complete physical exam during the screening period (both arms). Clinically significant abnormal findings should be recorded as medical history. An additional full physical exam should be performed at the end of trial intervention (Arm A). After the first dose of study treatment new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay attention to clinical signs related to previous serious illnesses.

6.1.2.3 Directed Physical Exam

A directed physical exam should be performed at Day 1 Cycle 1 (Arm A). During the course of active treatment, the Investigator or qualified designee will perform a directed physical exam as clinically indicated and according to site specific routine. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay attention to clinical signs related to previous serious illnesses.

6.1.2.4 Vital Signs

The Investigator or qualified designee will take vital signs at screening for patients of both arms. In addition, for patients in Arm A prior to the administration of study treatment (Day 1 Cycle 1) and at the end of trial intervention. During the course of active treatment, the Investigator or qualified designee will take vital signs as clinically indicated and according to site specific routine and will record abnormal findings only if clinically significant. Vital signs should include temperature, pulse, weight and blood pressure. Height will be measured at screening only.

6.1.2.5 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at screening (both Arms). For Arm A, ECG should be repeated prior to the first administration if screening ECG is older than

8 weeks, at least once during treatment at cycle 7 and at discontinuation of trial intervention and whenever clinically indicated using local standard procedures. Clinically significant abnormal findings from screening visit should be recorded as medical history, clinically significant abnormal findings during treatment should be recorded as adverse event.

6.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess the ECOG status (see Appendix 1) at screening and every three months thereafter for the first 2 years after randomization.

6.1.2.7 Tumor Imaging and Assessment of Disease

Tumor imaging is recommended to be acquired by computed tomography (CT). Magnetic resonance imaging (MRI) may be alternatively used when CT with iodinated contrast is contraindicated, when local practice mandates it or if clinically appropriate. It is recommended to use the same imaging technique regarding modality, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment. Imaging should include the chest, abdomen, and pelvis at baseline to ensure absence of disease and it is recommended to continue with this assessment for all subsequent imaging time points.

Participant baseline and follow-up imaging will be determined using local assessment (Investigator assessment), which in case of this trial is equal to evidence of new (previously untreated) lesions during study conduct. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

6.1.2.7.1 Initial Tumor Imaging

Initial tumor imaging at Screening will only be performed if last available tumor imaging is older than 10 weeks. The study team must review screening images to confirm the participant has no clinical or radiological evidence of disease (if images were obtained after treatment of metastatic disease) or all known lesions have been treated in the meantime.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they cover thorax and abdomen and not older than 10 weeks prior to the start of study intervention.

Tumor imaging prior to the definite treatment of colorectal cancer metastases as well as follow-up images should be (additionally if applicable) provided for centrally assessing the local control of lesions according to ablative technique (surgery vs. ablation vs. radiation).

6.1.2.7.2 Tumor Imaging During the Study

On-study imaging will be performed every 3 months (q3mo. ± 2 weeks) starting from the day of randomization and regardless of treatment cycle time points (Arm A) for the first two years after randomization and every 6 months (q6mo. ± 1 months) thereafter calculated from the date of the last imaging, respectively. Imaging can be performed more frequently if clinically indicated and complemented with ultrasound assessments in the intervals if indicated by the judgement of the investigator. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts (Arm A). Imaging should continue to be performed until relapse is identified by the Investigator or the patients has been observed for at least 5 years after randomization.

6.1.2.7.3 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging every 3 months (q3mo. ± 2 weeks) within the first two years after randomization and every 6 months (q6mo. ± 1 months) thereafter to monitor disease status until disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

6.1.2.7.4 Radiologic Assessment of Disease

Tumor images will be assessed by the local investigator for tumor relapse. The individual judgement of the investigator will serve as the basis for all protocol guidelines related to disease status (e.g. continuation or discontinuation of study intervention).

6.1.2.8 Covid-19 policy

Assessment of Covid-19 should be conducted according to the actual pandemic situation AND institutional policy that is applied to any patient that receives FOLFOX/FOLFOXIRI for colorectal cancer outside the trial. This may require assessment of vaccination status, physical examination, anamnesis and Covid-19 tests (e.g. antigen test and/or PCR testing). SARS-CoV-2-positive (without exceptions no matter if symptomatic or without symptoms) patients should not participate in the trial or chemotherapy application should be delayed as long as the patient is positive for SARS-CoV-2. Respective assessments should be repeated at any time if the investigator judgement, particularly in cases that present with new or changed risk factors (efficacy of vaccines, contact with infected patients etc).

6.1.3 Clinical Safety Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below and timing and frequency is specified in the Schedule of Trial Activities (Section 2.3).

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- If laboratory values from non protocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded on the appropriate eCRF page.
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Laboratory tests for hematology, chemistry, and others are specified within the Visit Requirements in Section 6.1.5.

Laboratory tests for screening should be performed within 7 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 24 hours prior to dosing. Results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to each dose of study treatment.

6.1.4 Other Procedures

6.1.4.1 Withdrawal/Discontinuation

Participants who withdraw prior to completion of the trial should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2.

6.1.4.2 Withdrawal from Translational Research / Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator. The investigator will inform the Sponsor. It is the responsibility of the investigator to subsequently inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request for withdrawal being received will continue to be used as part of the overall research study data and results. No new analyses should be generated after the request is received.

In the event that the specimens have been completely anonymized, there will be no link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

6.1.5 Visit Requirements

Visit requirements are outlined in the Schedule of Trial Activities in Section 2.3. Specific procedure-related details are provided above in the Section 6.1.1 – Section 6.1.4.

6.1.5.1 Screening and Randomization

Inclusion is possible 3-10 weeks after the SOC intervention after successful screening:

- Obtain informed consent.
- Check of Inclusion/Exclusion criteria.
- Review / documentation of demographics and medical history.
- Review / documentation of prior and concomitant medication.
- Review of prior FOLFOX(IRI) or CAPOX/XELOX therapy
- Baseline tumor imaging (separate tumor imaging at Screening will only be performed if last available tumor imaging is older than 10 weeks.)
- Carcinoembryonic antigen
- 12-Lead Electrocardiogram.

At maximum 14 days before first administration of study medication:

- ECOG performance status.
- Full physical examination.
- Review of adverse events
- Height, weight and vital signs (should include temperature, pulse and blood pressure).

At maximum 7 days before first administration of study medication:

- WOCBP only: Pregnancy Test – urine or serum β-HCG
- Coagulation (Quick's time [PT/INR], aPTT).
- CBC with differential:
  White Blood Cell (WBC) count with differential and Absolute Neutrophil Count (ANC); Absolute Lymphocyte Count (ALC); Red Blood Cells (RBCs); Platelet count; Hemoglobin; Hematocrit.
- Comprehensive serum chemistry panel:
  Alkaline phosphatase; Aspartate aminotransferase (AST); Potassium; Sodium; Total Bilirubin; Direct Bilirubin (if total bilirubin is elevated above the upper limit of normal); Creatinine.
- Assessment of Covid-19 should be conducted according to the actual pandemic situation AND institutional policy that is applied to any patient that receives

FOLFOX/FOLFOXIRI for colorectal cancer outside the trial. This may require assessment of vaccination status, physical examination, anamnesis and Covid-19 tests (e.g. antigen test and/or PCR testing). SARS-CoV-2-positive patients should not participate in the trial or chemotherapy application should be delayed as long as the patient is positive for SARS-CoV-2.

<u>After all screening assessments have been performed and results are available to confirm inclusion/exclusion criteria:</u>

- Randomization

6.1.5.2 Trial Intervention (Arm A only)

Trial intervention should start as close to the randomization as possible. The following is performed as part of the trial intervention for subjects in Arm A only.

<u>At maximum 72 hours before Day 1 of Cycle 1:</u>

- WOCBP only: Pregnancy Test – urine or serum β-HCG
- Quick's time [PT/INR] (only in case of concomitant use of 5-FU and oral anticoagulants)
- CBC with differential:
  White Blood Cell (WBC) count with differential and Absolute Neutrophil Count (ANC); Absolute Lymphocyte Count (ALC); Red Blood Cells (RBCs); Platelet count; Haemoglobin; Haematocrit.
- Comprehensive serum chemistry panel:
  Alkaline phosphatase; Aspartate aminotransferase (AST); Potassium; Sodium; Total Bilirubin; Direct Bilirubin (if total bilirubin is elevated above the upper limit of normal); Creatinine.

<u>Day 1 of Cycle 1(assessments can be performed up to 2 days before application of drugs):</u>

- Assessment of Covid-19 should be conducted according to the actual pandemic situation AND institutional policy that is applied to any patient that receives FOLFOX/FOLFOXIRI for colorectal cancer outside the trial. This may require assessment of vaccination status, physical examination, anamnesis and Covid-19 tests (e.g. antigen test and/or PCR testing). SARS-CoV-2-positive patients should not participate in the trial or chemotherapy application should be delayed as long as the patient is positive for SARS-CoV-2.
- Directed Physical Examination.
- Weight and Vital Signs (temperature, pulse and blood pressure).
- 12-Lead Electrocardiogram, only if ECG from screening is older than 8 weeks.

- Review / documentation of prior and concomitant medication
- Administration of mFOLFOXIRI or mFOLFOX-6 or de-escalated treatment regimens, if applicable.

Day 1 of Cycle 2-12 (assessments can be performed up to 2 days before application of drugs):

- Assessment of Covid-19 should be conducted according to the actual pandemic situation AND institutional policy that is applied to any patient that receives FOLFOX/FOLFOXIRI for colorectal cancer outside the trial. This may require assessment of vaccination status, physical examination, anamnesis and Covid-19 tests (e.g. antigen test and/or PCR testing). SARS-CoV-2-positive patients should not participate in the trial or chemotherapy application should be delayed as long as the patient is positive for SARS-CoV-2.
- Review / documentation of prior and concomitant medication
- Administration of mFOLFOXIRI or mFOLFOX-6 or de-escalated treatment regimens, if applicable.

During Cycle 2-12:

- WOCBP only: Pregnancy Test – urine or serum β-HCG – to be performed at every second cycle (at least monthly) during treatment and until the end of relevant systemic exposure to the study drug (i.e. ~30 days after the last dose), in accordance with the CTFG guidance on contraception.
- Quick's time [PT/INR] (only in case of concomitant use of 5-FU and oral anticoagulants)
- Directed Physical Examination.
- Weight and Vital Signs (temperature, pulse and blood pressure).
- 12-Lead Electrocardiogram at Cycle 7
- CBC with differential.*
- Comprehensive serum chemistry panel.*

*besides the frequency of the laboratory assessments, which should be scheduled according to study site standards or as clinically indicated, also the type of lab parameters to be tested should follow study site standards.

End of trial intervention:

- Full Physical Examination
- Weight and Vital Signs (temperature, pulse and blood pressure)
- 12-Lead Electrocardiogram
- Quick's time [PT/INR] (only in case of concomitant use of 5-FU and oral anticoagulants)
- CBC with differential:

White Blood Cell (WBC) count with differential and Absolute Neutrophil Count (ANC); Absolute Lymphocyte Count (ALC); Red Blood Cells (RBCs); Platelet count; Haemoglobin; Haematocrit.

- Comprehensive serum chemistry panel:
  Alkaline phosphatase; Aspartate aminotransferase (AST); Potassium; Sodium; Total Bilirubin; Direct Bilirubin (if total bilirubin is elevated above the upper limit of normal); Creatinine.

6.1.5.3 Structured Follow-up (Arm A and B)

To be performed as part of the structured follow-up.

Every 3 months during the first 24 months after randomization:

- ECOG Performance Status
- Review Adverse Events (at each visit during trial intervention for Arm A)
- Further anticancer therapy status (to be documented if and when new anticancer therapy (systemic and/or local) is initiated at the study site or if and when such information becomes available to the investigator, in case a new therapy is started somewhere else). All available information should be collected.
- EQ5D5L Questionnaire
- Tumor Imaging
- Carcinoembryonic antigen

Every 6 months for up to 60 months after randomization:

- Survival status
- EQ5D5L Questionnaire
- Tumor Imaging
- Carcinoembryonic antigen

6.2 Assessment of Safety

The respective SmPCs of routine chemotherapy medications will be used as reference documents and will be provided to the investigators in the investigator's site file.

6.2.1 Adverse Events and Laboratory Abnormalities Reporting

It is the responsibility of the investigators to document all adverse events, pregnancy and overdose in the eCRF. Any serious adverse event (SAE) must be reported immediately, without undue delay, but not later than 24 hours after obtaining knowledge to the CRO who will forward the SAEs to the Sponsor/Sponsor Representative within one working day.

6.2.1.1 Definitions

6.2.1.1.1 Adverse Event

An adverse event (AE) is defined in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment." (ICH E6: section 1.2).

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (including a worsening in the character, frequency, of severity of a pre-existing illness) temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

6.2.1.1.2 Adverse Drug Reaction

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose administered” (European Directive 2001/20/EC).

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event 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).

6.2.1.1.3 Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence (adverse event) that at any dose

- results in death
- is life-threatening (subject was at immediate risk of death at the time of the event)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another significant medical condition/event

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 i.e. important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require interventions to prevent one of the other outcomes listed above (e.g. emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the "other significant medical condition" criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Hospitalization for performing of protocol-required procedures or administration of study treatment or hospitalizations for procedures planned prior to study start and elective hospitalizations are not classified as an SAE, however any AE that occurs during this hospitalization and meets any of the above mentioned criteria of seriousness needs to be reported as SAE.

Any second primary malignancy occurring in a patient during or after study treatment within the safety reporting period will be assessed as important medical event and thus has to be reported as SAE.

Progression of the underlying malignant disease and symptoms caused by progression of the underlying tumor disease need not to be reported as SAE in this protocol, unless progression or symptoms of progression are assessed as causally related to study medication.

6.2.1.1.4 Unexpected Adverse Event / Suspected Unexpacted Serious Adverse Reaction

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current version of the respective SmPCs of routine chemotherapy medications. Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. An event more specific or more severe than described in the current version of the respective SmPCs of routine chemotherapy medications would be considered "unexpected".

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction, the nature or severity of which is not consistent with the applicable safety reference document (SmPC). All suspected adverse reactions related to study medication which occur in this trial and are both unexpected and serious (SUSARs) are subject to expedited reporting.

SAEs which are "serious", "related" and "unexpected" meet the criteria for SUSAR.

In case of SUSARs a CIOMS report is completed and forwarded to the competent authorities, all participating investigators and the Sponsor. According to § 13 of the GCP guideline SUSAR reporting occurs immediately, but no later than 15 calendar days. Reporting of life-threatening or fatal SUSARs occurs immediately, but no later than 7 calendar days.

6.2.1.2 Adverse Events Reporting

All adverse events are documented by the participating site in the patient’s medical records and the eCRF. AEs are assessed from date of first study treatment until 4 weeks after the last dose of study therapy at every visit. For Arm B in which patients are not being actively treated, adverse events should be queried at every visit (planned and unplanned) during the first 7 months from randomization, but at least twice (i.e. at the 3 and 6 months visit). Thereafter, adverse events should be queried every three months for both groups by an unbiased open question for up to two years after randomization.

In addition to the documentation in the eCRF, all SAEs are reported by the site immediately, without undue delay, but not later than 24 hours after obtaining knowledge to the CRO by fax or email.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by patient are properly captured in the patients' medical records (source data).

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

- Adverse event diagnosis or syndrome(s), preferably as term, if known, otherwise if not known signs or symptoms
- Event description (with detail appropriate to the event)
- Date of onset (if applicable, date of becoming serious)
- Date of resolution
- Seriousness (yes/no) / seriousness criterion (in case of AE fulfils criteria of SAE, SAE reporting is required)
- Treatment required
    - None
    - Drug Treatment
    - Intensive Care
    - Other
- Severity (Grade according to CTCAE version 5 or if not specified in CTCAE as follows):
    - Grade I: mild (awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities)
    - Grade II: moderate (discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic maneuvers)
    - Grade III: severe (incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required)
    - Grade IV: life-threatening (immediate risk of death; requires hospitalization and clinical intervention)
    - Grad V: death)
- Assessment of relatedness to study treatment (related/not related)
- Outcome:
    - Recovered/resolved
    - Recovering/resolving/ongoing
    - Recovered/resolved with sequelae
    - Not recovered/not resolved
    - Fatal
    - Unknown (only applicable if patient is lost to follow-up)

- Action taken regarding study drugs:
- None
    - Dose reduced (new dose)
    - Dose increased
    - Temporarily discontinued (stop date, date of re-start)
    - Permanently discontinued (stop date)
    - Not applicable
    - Unknown.

Medically significant adverse events considered related to the investigational product by the investigator, coordinating investigator or the Sponsor will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related or of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-treatment (EOT) assessment and be under medical supervision until symptoms cease or the condition becomes stable.

All clinical adverse events (AEs) encountered during the clinical study will be reported on the AE page of the eCRF.

Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5 (Appendix 2).

Progression or deterioration of the malignancy under study (including new metastatic lesions and death due to disease progression) will be part of the efficacy assessment and should **NOT** be reported as AE or SAE.

6.2.1.3 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the eCRF. Laboratory test value abnormalities as such should be considered as an AE in case they are:

- Accompanied by clinical symptoms.
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation).
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

In general, it is the investigator's responsibility to review all abnormal laboratory results and to determine if a given value represents a clinically significant change compared to previously obtained values and results in an adverse event (AE) or not.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an adverse event in the eCRF.

6.2.2 Handling and Reporting of Safety Parameters

6.2.2.1 Serious Adverse Events

For each patient any clinical adverse event or abnormal laboratory test value that is serious occurring during the course of the study from the date of first study treatment until up to 4 weeks after the last dose of study treatment, must be reported immediately, without undue delay, but not later than 24 hours after recognition or receiving knowledge to CRO via fax or email with a completed SAE Report Form to the Sponsor and coordinating investigator. If missing information about a SAE cannot be collected, the SAE should be reported immediately, without undue delay, but not later than 24 hours and the missing information sent later as a follow-up report as soon as possible.

The coordinating investigator as the sponsors authorized representative will medically review all SAE reports (second assessment of the SAE) within 3 calendar days, for fatal and life-threatening SAEs within one calendar day, with regard to:

- Relationship to study treatment
- Expectedness
- Change of risk-benefit relation of the study

The Sponsor and the CRO will ensure compliance with all regulatory reporting requirements including the notification of the appropriate Ethics Committees, Competent Authorities and participating investigators of all serious adverse events occurring at the sites in accordance with national laws of Germany, ICH Good Clinical Practice and European/EMA requirements.

Expectedness of any SAE will be assessed by means of the reference safety information in the current version of the respective SmPC for standard chemotherapy medications. Every SAE, being assessed by either the investigator or the sponsor (respectively the coordinating investigator) as related to study drug und assessed as being either unexpected or unexpected with regard to outcome or severity of the event will be reported as SUSAR to the competent authorities, responsible ethics committee and investigators of the trial in line with the national regulations in effect (German drug law [AMG] and GCP-V).

Fatal or life-threatening SUSARs must be reported within 7 days, all others need to be reported within 15 days. Also, all events which can change the risk-benefit ratio of the study drug have to be reported within 15 days in the same way as SUSARs.

Once a year throughout the clinical trial or on demand, the sponsor will provide the competent authorities and the responsible ethics committee with the annual safety report in the format of the Development Safety Update Report (DSUR) in accordance with European and national regulations (GCP-V).

Misuse, abuse and overdose of study medication (i.e. higher dose than stipulated by the protocol) have to be reported to the Sponsor and the CRO within 15 days of identification.

Cases of misuse, abuse or overdose that lead to serious adverse reactions should be reported on an expedited basis with a completed and faxed or emailed SAE Report Form.

6.2.2.2 Treatment and Follow-up of Adverse Events

Adverse events, especially those for which the relationship to the study medication is related, should be followed up until they have returned to baseline status or stabilized. If a clear explanation is established, it should be recorded on the eCRF.

6.2.2.3 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the eCRF.

6.2.2.4 Adverse drug reactions with Concomitant Medication

The investigators must be aware that for all concomitant medications the regulations of post marketing reporting for suspected adverse drug reactions apply, i.e. reporting to the marketing authorization holder or the local regulatory bodies.

6.2.2.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the sponsor or designee.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious adverse events. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

SAE reports and any other relevant safety information are to be forwarded to the Institut für Klinische Krebsforschung IKF GmbH:

IKF Safety facsimile number: +49 / (0)69 / 7601 – 3655

or

email: sae@ikf-khnw.de

7 Accompanying Translational Research Project

The accompanying translational research project aims to identify and characterize molecularly-defined patient subgroups and to correlate their genetic and molecular tumor characteristics with clinical efficacy and toxicity using tumor specimen and blood-based biomarker candidates. Participation in translational research projects is optional for the patient and requires separate consent. If the patient does not consent or withdraws consent, this will have no impact on the study participation nor on his / her treatment outside this study.

7.1 Sampling Time Points, Materials and Analyses

Tissue and blood samples should be sent to:

Prof. Dr. med. Dominik Modest
Keyword: PORT
Medizinische Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie
Campus Virchow Klinikum (CVK)
Geländeaddresse: Ostring 1; DG, Studienzentrale
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin

7.1.1 Processing and Storage of blood samples

- Streck tubes might be shipped without refrigeration at any time.
- EDTA and serum blood should be processed with centrifugation, filled in sample tubes and stored at -20°C or below that temperature. Shipment of EDTA/Serum samples should be conducted in larger cohorts and coordinated with the sponsor representative to ensure arrival at workdays and continuous cooling.
- An additional graphical illustration is part of the study documents for the processing and shipment of samples.

7.1.2 Tissue Samples

Formalin-fixed, paraffin embedded (FFPE) tissue blocks – blocks are preferred over slides – will be collected at baseline and after relapse of disease if a new biopsy or a new block of tissue is obtained within the clinical routine. Samples should be obtained by core or excisional biopsies (fine needle aspiration and bone metastasis samples are not acceptable) of a tumor lesion not previously irradiated. Tissue samples should be sent in pairs (if available) for any patient directly to the sponsor representative (see above).

7.1.3 Blood Samples

EDTA blood (10 ml), serum (10 ml) and Streck tubes (10 ml) samples are taken at Screening and every three months during the first 24 months after randomization and every 6 months thereafter - as long as no relapse occurs.

7.1.4 Analyses

The translational research projects might be adjusted or expanded taking the latest research data into account, but will consist of the following steps:

1. Characterization of the initial resected/ablated tumor (primary and/or metastases) for DNA mutations and RNA expressions (for example panel NGS and mRNA expression analysis)
2. Sequential central assessment of tumor markers and circulating tumor DNA (according to initial tumor characteristics), including three assessments during study intervention (baseline, after 3 months, after 6 months).
3. Characterization of tumor specimen obtained after relapse of disease during or after study (if occurring and available) for DNA mutations and RNA expressions.
4. Correlation of 1) with 3) and eventually also correlation of relapse tumor tissue with acquired changes in samples of 2)

This paired sample collection including relapse specimen plus the longitudinal assessment of circulating tumor DNA will be performed in order to inform about early detection of relapse (potentially prior to radiographic correlate), relapse patterns (based on initial spread and the ablative technique) and molecular background of relapse (tumor evolution, secondary mutations, expressions).

8 Statistical Analysis

8.1 Justification of Sample Size

The primary endpoint will be PFS (progression-free survival, defined as progression/relapse or death from any cause) at 24 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 monotherapies [Mitry et al., 2008] 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 trial. 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 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 arm [Mitry et al., 2008]). With a hazard ratio 0.70 (=λ_I/λ_C C=0.0267/0.0382) favoring active treatment, the hypothesized relapse rate at 24 months in 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 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.

8.2 Analysis

Statistical analysis is based on the International Conference on Harmonization (ICH) Guidelines “Structure and Content of Clinical Study Reports” and “Statistical Principles for Clinical Trials”. No interims analysis is planned. Prior to the final analysis, data will be verified with respect to completeness and plausibility (data cleaning). Inconsistencies and mistakes will be clarified with the study sites and will be removed. The data cleaning process starts soon after first patients are enrolled and monitored. Major protocol violations and special cases will be listed. Prior to the final analysis, a conference with coordinating investigator, statistician, and the steering committee of the study will discuss and define the statistical analysis plan (SAP) and the handling of special cases and major violations. This conference will also define those violations, which will result in the exclusion from the per protocol (PP) population or even from the intent-to-treat (ITT) population. Exclusion from the ITT group is limited to very special cases such as patients with the incorrect disease.

Primary analysis:

The null hypothesis to be tested in confirmatory analysis states that the hazard ratio for PFS comparing intervention versus control equals 1. This hypothesis will be tested by means of Cox-regression adjusting for the strata for randomization. The two-sided significance level is set to 0.05. The Cox-regression adjusted for additional factors provides a power advantage compared to the logrank test used for sample size calculation and this procedure thus provides a conservative approach. The primary analysis will be conducted based on the full analysis set which is defined as the Intent-to-treat population including all randomized patients. In a survival analysis setting, missing values are treated as non-informative censoring values so there is no need for imputation.

Secondary analyses:

As a sensitivity analysis to the primary efficacy analysis, the same test will be repeated on the per-protocol population. As another sensitivity analysis, the primary hypothesis will also be tested with the test for the average hazard ratio to potentially account for non-proportional hazards [Rauch et al., 2018]. Event probabilities of PSF will be estimated by Kaplan-Meier-Curves. The above analyses will be repeated for overall survival (OS). The influence of treatments received after the period of intervention on (PFS and) OS will be assessed. Specific post-study treatments will be included in a Cox model as time-dependent explanatory variables. Longitudinal models will be fitted to examine the evolution over time of the two arms and to test potential differences between them. Circulating tumor DNA, tumors markers and molecular information as well as Quality of life/ patient reported outcomes will be evaluated exploratory.

Safety analyses:

Safety analysis will be performed in the safety set. Absolute and relative frequencies as well as unbiased event-rate estimates (Kaplan-Meier, Empirical cumulative incidence) of AEs, SAEs, event rates of grade 3 and 4 toxicities (NCI-CTCAE) and abnormal laboratory values/ increase/decrease between treatment arms will be reported at different time points together with 95%-confidence intervals.

A detailed methodology for the statistical analysis will be described in the statistical analysis plan (SAP), which will be finalized before database lock. This also includes specification of validated statistical software to be used for analysis.

8.2.1 Study Populations for Analysis

The following data sets for analysis are defined:

Intent-to-treat population (ITT):

The intent-to-treat (ITT) population includes all randomized patients. Treatment assignment is based on the randomized treatment (primary population). The ITT population is the primary

population for the description of the patient and treatment characteristics and is used for the primary efficacy analysis.

Per-protocol (PP) population:

This population will include all randomized patients fulfilling the inclusion and exclusion criteria and who received at least one cycle of active treatment with at least one documented structured follow-up visits (Arm A) or with at least one documented follow-up visit (Arm B). Treatment assignment is based on the treatment actually received.

Safety analysis set:

The safety population for chemotherapy related toxicities comprises all patients who received at least one administration of mFOLFOXIRI/mFOLFOX-6 after randomization.

Several subgroup analyses including but not limited to prior systemic therapy (with vs. without prior systemic therapy), resection status (R1 vs. R0 resected lesions) and type of definite treatment of colorectal cancer metastases (ablated vs. purely resected lesions) are planned. In addition, and more explorative, subgroups might be defined based on circulating tumor DNA status at baseline (ctDNA positive vs. negative) and other molecular parameters. Further details will be specified in the SAP.

8.3 Further Analysis

In addition, multiple types of machine learning (ML) models will be retrospectively applied on the data to evaluate the potential of ML-algorithms in predicting the occurrence of the primary as well as secondary endpoints on an exploratory basis. The ML models will use all categorical and numerical data outlined above and supervised and unsupervised learning models shall be tested. For analysis, model selection and hyperparameter optimization, the baseline dataset will be split into training and evaluation data using stratified k-fold crossvalidation. For supervised binary classification (e.g. PFS within 24 months) *Logistic Regression*, *Support Vector Classifier* and *Neural Networks* will be performed. Unsupervised learning algorithms will entail *K-Nearest Neighbor* or a *Gaussian Mixture Model* after principal component analysis.

The evaluation of ML-algorithms with respect to their test performance criteria will be conducted using receiver operating characteristic (ROC) curves, which indicate the discriminatory power of a diagnostic test. The ROC curve describes the dependence of sensitivity (true positive rate) and 1-specificity (false positive rate) for different threshold values of the ML classifier. The Area Under the Curve (AUC) of the ROC will subsequently be applied to quantify the classification performance of each model at all classification thresholds. Depending on the balance of the dataset, precision-recall AUC will additionally be used for classifier performance testing.

Data cleaning and preprocessing will be conducted with Python using the *Anaconda/Jupyter-Notebook* (Anaconda Inc., Austin, TX, USA). ML algorithm calculation and testing will be performed with SKLearn [Buitinck et al., 2013]. Modelling of Neuronal Networks in particular will furthermore require Tensor Flow [Abadi et al., 2016].

9 Study Medication

This section provides an overview on the study medication used. It is not intended to replace the careful reading of the summary of product characteristics (SmPC) for each component, which contains details on drug characteristics, storage, application, mode of action and adverse reactions. All substances within the FOLFOX / FOLFOXIRI regimen are market approved in Germany/Europe for at least one kind of tumor. Moreover, the regimens are standard of care for patients with of lower stages of colorectal cancer. Therefore, the protocol requires limited documentation of concomitant medication with regard to FOLFOX / FOLFOXIRI in this trial. If patients receive concomitant medication, the product characteristics need to be checked by the investigator with respect to potential drug interactions. In case of any doubt, the lead coordinating investigator shall be consulted. The investigator or the pharmaceutical expert in delegation is responsible for the safe storage, preparation, release, and documentation of the study medication with respect to standard procedures and national guidelines. All medication shall be distributed according to the prescription of the investigator

9.1 mFOLFOX-6

9.1.1 Oxaliplatin

Oxaliplatin (trade name: e.g. Eloxatin®) is presented as a clear, colourless concentrate in glass vials of 20 mL containing 100 mg active compound and to be diluted for preparation of an infusion solution. Oxaliplatin will be administered in 500mL of 5% glucose solution as a two-hour i.v. infusion. Oxaliplatin should always be administered before 5-FU. For further information see the respective SmPC (Summary of Product Characteristics, *Fachinformation*). 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, initial diluted solution, or infusion solution should come into contact with skin, immediately and thoroughly wash with soap and water. If oxaliplatin concentrate, initial diluted solution, or infusion solution should come into contact with mucosa, immediately and thoroughly wash 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 / administration needles or intravenous administration sets containing aluminium parts, as aluminium has been reported to cause degradation of platinum compounds.

9.1.1.1 Possible Adverse Effects of Oxaliplatin

Nausea/vomiting, diarrhea, leukopenia, thrombocytopenia, anemia, increase of liver enzymes, alopecia, peripheral neurotoxicity. Please refer to the respective SmPC for further details.

9.1.2 Leucovorin

Leucovorin (calcium folinate; e.g. Leucovorin 10mg/ml Pfizer) is administered intravenously according to the respective package insert and local routine.

9.1.2.1 Possible Adverse Effects of Leucovorin

Rare adverse effects related to Leucovorin are: Central nervous and/or gastrointestinal disturbances, allergic reactions. Please refer to the respective SmPC for further details.

9.1.3 5-Fluorouracil

5-Fluorouracil (e.g. 5-FU; e.g. 5-FU 50mg/ml Medac) is administered intravenously as described in section 10 (Therapy schema), according to the respective package insert and local routine at the respective study site.

Fluorouracil (5-FU) must not be given in combination with brivudin, sorivudin and analogues. Brivudin, sorivudin and analogues are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD). Fluorouracil (5-FU) must not be given to patients homozygotic for dihydropyrimidine dehydrogenase [mutations] (DPD). Where applicable, determination of DPD enzyme activity is indicated before starting treatment with 5-fluorpyrimidines.

9.1.3.1 Possible Adverse Effects of 5-Fluorouracil

Nausea/vomiting, diarrhea, mucositis, hand-foot-skin-reactions, disturbances in cardiac function, skin alterations, alopecia, hematotoxicity. Please refer to the respective SmPC (Fachinformation) for further details.

9.2 mFOLFOXIRI

See section above for details on Oxaliplatin (Section 9.1.1), Leucovorin (Section 9.1.2) and 5-Fluorouracil (Section 9.1.3).

9.2.1 Irinotecan

Irinotecan is in topoisomerase inhibitor and works by blocking topoisomerase 1 which results in DNA damage and cell death. Irinotecan is administered intravenously according to the respective package insert and local routine.

9.2.1.1 Possible Adverse Effects of Irinotecan

Common side effects include diarrhea, vomiting, bone marrow suppression, alopecia, shortness of breath, and fever. Other severe side effects include blood clots, colon inflammation, and allergic reactions. Please refer to the respective SmPC for further details.

10 Administrative and Regulatory Details

10.1 Regulatory and Ethical Compliance

This clinical trial was designed and shall be implemented and reported in accordance with the protocol, the AMG (Arzneimittelgesetz), the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

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 his or her 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 an adverse drug event, the patient should inform the Investigator about this fact.

10.2 Registration and Request for Authorization of the Trial

According to GCP-V, the trial has to be submitted to and to be authorized/approved by the competent authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) and the Ethics Committee(s) responsible for the trial. The respective local authorities will be informed about the trial and the participation of individual trial sites.

The competent authority and the competent Ethics Committee will be informed on the course of the study with respect to safety aspects to be announced as well as on the termination of the trial and the trial results according to GCP-V.

10.3 Ethics Committee

Prior to start of the trial the study protocol and all additionally relevant documents will be sent by the Sponsor or designee to the competent Ethics Committee in order to receive the committee's opinion. The trial is only allowed to start after a positive vote of the Ethics Committee has been received. During the course of the study the Sponsor or designee will inform the Ethics Committee about all amendments to the study protocol as well as on all SUSARs emerging from the trial according to GCP-V. In addition, the competent ethical committee will receive a DSUR once a year.

All subsequent protocol amendments and amendments to the informed consent form will be submitted to the competent Ethics Committee to obtain an updated vote before implementation of the changes. Serious or unexpected adverse events occurring during the trial likely to affect the safety of the subjects or the conduct of the trial will also be reported to the Ethics Committee.

In addition, the competent Ethics Committee will be informed on the course of the study with respect to the termination of the trial and the trial results.

10.4 Informed Consent

It is the Investigator's responsibility to obtain witnessed written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial and before any trial specific procedures are performed. The patient should be given a copy of the informed consent documentation. The wet ink copy of the signed and dated informed consent must be retained in the institution's records and is subject to inspection by representatives of the Sponsor or representatives from regulatory agencies.

10.5 Insurance

A clinical trials insurance is contracted in accordance with the local law before submission of the study to the relevant authorities. A copy of the confirmation and the conditions of the insurance will be handed out to every trial subject together with the informed consent form.

10.6 Confidentiality

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor or designee will be maintained in confidence, and such information will be divulged to the local Ethics Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the Investigator, except to the extent that it is included in a publication as provided in Section 10.12 of this protocol.

10.7 Confidentiality of Subject Records

By signing this protocol, the Investigator agrees that the Sponsor (or designee), EC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by the screening or trial subject number only; full names/initials will be masked prior to transmission to the Sponsor or designee.

By signing this protocol, the Investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.8 Confidentiality of Investigator Information

By signing this protocol, the Investigator recognizes that certain personal identifying information with respect to the Investigator, and all Sub-Investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of regulatory submissions, and as required by law. This information may include:

1. Name, address, telephone number and e-mail address;
2. Hospital or clinic address and telephone number;

3. Curriculum vitae or other summary of qualifications and credentials; and
4. Other professional documentation.

Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other Investigators. By signing this protocol, the Investigator expressly consents to these uses and disclosures.

As this is a multicenter trial, in order to facilitate contact between Investigators, the Sponsor or designee may share an Investigator's name and contact information with other participating Investigators upon request.

10.9 Compliance with Financial Disclosure Requirements

The Investigator/Sub-Investigator(s) agree to provide his/her financial interests in and/or arrangements with the Sponsor on a Financial Disclosure Form provided by the Sponsor or designee.

10.10 Quality Management System

10.10.1 Quality Control and Quality Assurance

The Standard Operating Procedures (SOPs) of the Sponsor or designee or its designated sub-contractors (if applicable) are used for conduction of the trial as specified in the respective agreements between the parties.

10.10.2 Audits and Inspections

In case of an audit/inspection by the Sponsor or designee or an appropriate authority, the investigator will make all relevant documents available. If an inspection visit by a regional authority is announced, the respective trial site should inform the Sponsor or designee as early as possible in order to allow for an appropriate preparation and support.

10.10.3 Monitoring

It is understood that an outside monitor and other authorized personnel may contact and visit the Investigator, and that they will be allowed direct access to source data/documents for trial-related monitoring, audits, EC review and regulatory inspection. Direct access is defined as permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical trial. All reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and Sponsor's proprietary information will be exercised (Guideline for Good Clinical Practice, ICH Harmonized Tripartite Guideline, adopted July 1996: Chapter 5.15.1 and 1.21, respectively).

It is the monitor's responsibility to inspect the case report forms at regular intervals throughout the trial to verify adherence to the protocol: the completeness, accuracy, and consistency of the data; and adherence to Good Clinical Practice guidelines. The monitor should have access

to patient charts, laboratory reports and other patient records needed to verify the entries on the case report forms. Where local rules do not allow direct access to the source data, the monitor will verify entries in the case report form by asking direct questions of a person or persons with authorized access to the source data. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

A monitoring plan with relevant details will be issued and regularly updated throughout the trial.

An adjustment of monitoring activities to Covid-19 pandemic will be done due to actual recommendations and legal requirements. If on-site monitoring will not be possible at a certain point due to the pandemic, continuous monitoring of the data base will take place. Field monitors will be in close contact with the study sites to reschedule the planned on-site visits to the next possible date. Where remote monitoring can take place without loss of quality and oversight, e.g. in case of site initiation, it can replace regular on-site monitoring.

10.11 Data Management

Data collection and capture, creation of queries and data analysis will be performed by the Sponsor or designee or its designated sub-contractors (if applicable). Good Clinical Practice (GCP)-compliant handling of the data is secured by adequate SOPs. Archiving of data and results electronically recorded will be at least 15 years after the end of this study (according to legal guidelines).

10.11.1 Plausibility Check, Data Cleaning and Coding

Qualified members of the Sponsor or designee or its designated sub-contractors (if applicable) regularly perform plausibility checks and data cleaning according to the data-cleaning plan. Some of the raw data of the eCRF also needs coding (e.g., surgical procedures, toxicities) according to the data-coding plan. Before data base closure, data cleaning and manual plausibility checks have to be performed for the relevant contents (defined by the data-cleaning plan), and all open questions have to be resolved.

10.12 Publication and Registration of the Trial

The results of this trial will be published by the Coordinating Investigator and/or Sponsor after final analysis has been performed. Publication will be independent of the nature of the results obtained (whether they were positive or negative). The manuscript written for publication, together with the materials provided by the statistician can be accepted as the final study report.

This clinical trial will be registered at a primary register of the WHO, e.g. at www.clinicaltrials.gov.

10.13 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established, consisting of experts in clinical trials and medical oncology. The DSMB will receive regular information on safety results of the trial (SAEs/SUSARs) and recommend on the continuation, modification or early termination of the clinical trials at each meeting and according to the criteria defined by the sponsor. Furthermore, the DSMB will review the yearly safety report (DSUR) and provide recommendations to the sponsor.

Detailed working procedures are defined in the “Working Procedure for the Data Safety Monitoring Board (DSMB)”.

11 References

Abadi M, Agarwal A, Barham P, et al. **TensorFlow: large-scale Machine Learning on heterogeneous distributed Systems.** In arXiv:1605.08695. 2016

Andre T, Bensmaine MA, Louvet C, et al. **Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen.** J Clin Oncol, 1999; 17(11), 3560-3568.

Andre T, Louvet C, Maindrault-Goebel F, et al. **CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR.** Eur J Cancer, 1999; 35(9), 1343-1347.

Andre T, Boni C, Mounedji-Boudiaf L, et al. **Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.** N Engl J Med 2004; 350(23): 2343-51.

Buitinck L, Louppe G, Blondel, et al. **API design for machine learning software: experiences from the scikit-learn project.** European Conference on Machine Learning and Principles and Practices of Knowledge Discovery in Databases, Prague. 2013.

Carpizo DR, D'Angelica M. **Liver resection for metastatic colorectal cancer in the presence of extrahepatic disease.** Lancet Oncol 2009; 10(8): 801-9.

Choti MA, Thomas M, Wong SL, et al. **Surgical Resection Preferences and Perceptions among Medical Oncologists Treating Liver Metastases from Colorectal Cancer.** Ann Surg Oncol 2016; 23(2): 375-81.

Conroy T, Desseigne F, Ychou M, et al. **FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.** N Engl J Med 2011; 364(19): 1817-25.

Conroy T, Hammel P, Hebbar M, et al. **FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer.** N Engl J Med 2018; 379(25): 2395-406.

Cremolini C, Loupakis F, Antoniotti C, et al. **FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study.** Lancet Oncol 2015; 16(13): 1306-15.

Cremolini C, Casagrande M, Loupakis F, et al. **Efficacy of FOLFOXIRI plus bevacizumab in liver-limited metastatic colorectal cancer: A pooled analysis of clinical studies by Gruppo Oncologico del Nord Ovest.** Eur J Cancer 2017; 73:74-84.

de Gramont A, Vignoud J, Tournigand C, et al. **Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer.** Eur J Cancer 1997; 33(2), 214-219.

Ferlay J, Autier P, Boniol M, et al. **Estimates of the cancer incidence and mortality in Europe in 2006.** Ann Oncol 2007; 18(3), 581-592.

Folprecht G, Gruenberger T, Bechstein W, et al. **Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study).** Ann Oncol 2014; 25(5): 1018-25.

Garcia M, Jemal A, Ward E, et al. **Global Cancer Facts & Figures 2007.** Atlanta, GA; American Cancer Society 2007.

Gonzalez M, Poncet A, Combescure C, et al. **Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis.** Ann Surg Oncol 2013; 20(2): 572-9.

Grothey A, Sobrero AF, Shields AF, et al. **Duration of Adjuvant Chemotherapy for Stage III Colon Cancer.** N Engl J Med 2018; 378(13): 1177-88.

Heinemann V, von Weikersthal LF, Decker T, et al. **FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial.** Lancet Oncol 2014; 15(10): 1065-75.

Howlader N, Krapcho M, Neyman N et al. **SEER Cancer Statistics Review, 1975-2009** (Vintage 2009 Populations); Bethesda M: National Cancer Institute 2011.

Kopetz S, Chang GJ, Overman MJ, et al. **Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy.** J Clin Oncol 2009; 27(22): 3677-83.

Luo LX, Yu ZY, Huang JW, Wu H. **Selecting patients for a second hepatectomy for colorectal metastases: an systemic review and meta-analysis.** Eur J Surg Oncol 2014; 40(9): 1036-48.

Loupakis F, Cremolini C, Masi G, et al. **Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer.** N Engl J Med 2014; 371(17): 1609-18.

Maindrault-Goebel F, Louvet C, Andre T, et al. **Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6).** GERCOR. Eur J Cancer 1999; 35(9), 1338-1342.

Maindrault-Goebel F, de Gramont A, Louvet C, et al. **Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer.** Oncology Multidisciplinary Research Group (GERCOR). Ann Oncol 2000; 11(11), 1477-1483.

Maindrault-Goebel F, De Gramont A, Louvet C, et al. **High-dose intensity oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX 7).** European Journal of Cancer 2001; 37(8), 1000-1005.

Mitry E, Fields AL, Bleiberg H, et al. **Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials.** J Clin Oncol 2008; 26(30): 4906-11.

Modest DP, Denecke T, Pratschke J, et al. **Surgical treatment options following chemotherapy plus cetuximab or bevacizumab in metastatic colorectal cancer-central evaluation of FIRE-3.** Eur J Cancer 2018; 88: 77-86.

Nordlinger B, Sorbye H, Glimelius B, et al. **Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial.** Lancet 2008; 371(9617): 1007-16.

Nordlinger B, Sorbye H, Glimelius B, et al. **Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial.** Lancet Oncol 2013; 14(12): 1208-15.

Patel D, Townsend AR, Karapetis C, et al. **Is Survival for Patients with Resectable Lung Metastatic Colorectal Cancer Comparable to Those with Resectable Liver Disease? Results from the South Australian Metastatic Colorectal Registry.** Ann Surg Oncol 2016; 23(11): 3616-22.

Primrose J, Falk S, Finch-Jones M, et al. **Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial.** Lancet Oncol 2014;15(6):601-11.

Rauch G, Brannath W, Bruckner M, et al. **The Average Hazard Ratio - A Good Effect Measure for Time-to-event Endpoints when the Proportional Hazard Assumption is Violated?** Methods Inf Med 2018; 57(3): 89-100.

Robert Koch-Institut (Hrsg) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Hrsg). **Krebs in Deutschland für 2015/2016**. Berlin, 2019; 12. Ausgabe.

Saad ED, Katz A, Hoff PM, et al**. Progression-free survival as surrogate and as true end point: insights from the breast and colorectal cancer literature.** Ann Oncol. 2010;21(1):7-12.

Schmiegel W, Buchberger B, Follmann M, et al. **S3-Leitlinie – Kolorektales Karzinom.** Z Gastroenterol 2017; 55(12): 1344-498.

Schmoll HJ, Van Cutsem E, Stein A, et al. **ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making**. Ann Oncol 2012; 23(10), 2479-2516.

Soerjomataram I, Lortet-Tieulent J, Parkin DM, et al**. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions.** Lancet 2012; 380(9856): 1840-50.

Siegel R, Naishadham D & Jemal A **Cancer statistics, 2012.** CA Cancer J Clin 2012; 62(1), 10-29

Tournigand C, Andre T, Achille E, et al. **FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study.** J Clin Oncol 2004; 22(2), 229-237.

Van Cutsem E, Cervantes A, Adam R, et al. **ESMO consensus guidelines for the management of patients with metastatic colorectal cancer.** Ann Oncol 2016; 27(8): 1386-422.

12 Appendices

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Contraception Requirements

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below during the treatment period and for at least 180 days after the last administration of study drug.

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to use highly effective methods of contraception consistently during the treatment period and for at least 180 days after the last administration of study drug (i.e. mandatory condom use, mandatory use of effective methods of contraception for female partners of males

participating in the study as described in the table below, refrain from sperm donation for male participants during the treatment period and for at least 180 days after the last administration of study drug).

Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen-containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test. If applicable, this test should be repeated a maximum of 24 hours before the first dose.

Following initiation of treatment, pregnancy testing will be performed at monthly intervals during treatment and until the end of relevant systemic exposure to the study drug, in accordance with the CTFG guidance on contraception.

Appendix 4: Evaluation of radiologic images

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT scans are recommended to have slice thickness of < 5 mm. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible. As the primary endpoint of the trial is based on detection of relapse/progression of disease, different and changing modalities are permitted and unlikely to introduce bias.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, cytology and histology if clinically indicated and performed can be used to prove tumor relapse/progression. If relapse is proven/suspected by ultrasound, confirmation by CT/MRI should in any case be obtained.

IDENTIFICATION OF RELAPSE OR PROGRESSION

The definite decision to diagnose a relapse/progression should be made by the investigator, taking perspectives of the radiologist and/or the interdisciplinary tumor conference into account – if applicable. Relapse/progression can be diagnosed by solid metastases in organs like liver or lung or indirect signs (progressive ascites). In unclear cases, confirmation by biopsy might be considered, if possible. As long as uncertainty concerning the remission status must be stated, continuation of study therapy is recommended.

All potential new lesions should be evaluated as such. Measurements of all new lesions (or local progression) and involved organs is required and should be reported in the eCRF. Lymph nodes, particularly in local and timely connection to interventions, as site of relapse may only be considered definite lesions if they present with a short diameter of 15 mm or longer. All other relapses in lymph nodes require individual reporting and/or consultation with the sponsor representative. The total number of involved organs should be determined and also the total number of lesions (in case of more than 10 lesions, estimations are permitted)

NEW LESIONS

The appearance of new malignant lesions denotes disease progression/relapse; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be

unequivocal, that especially not represent something other than active tumor. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeated scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.