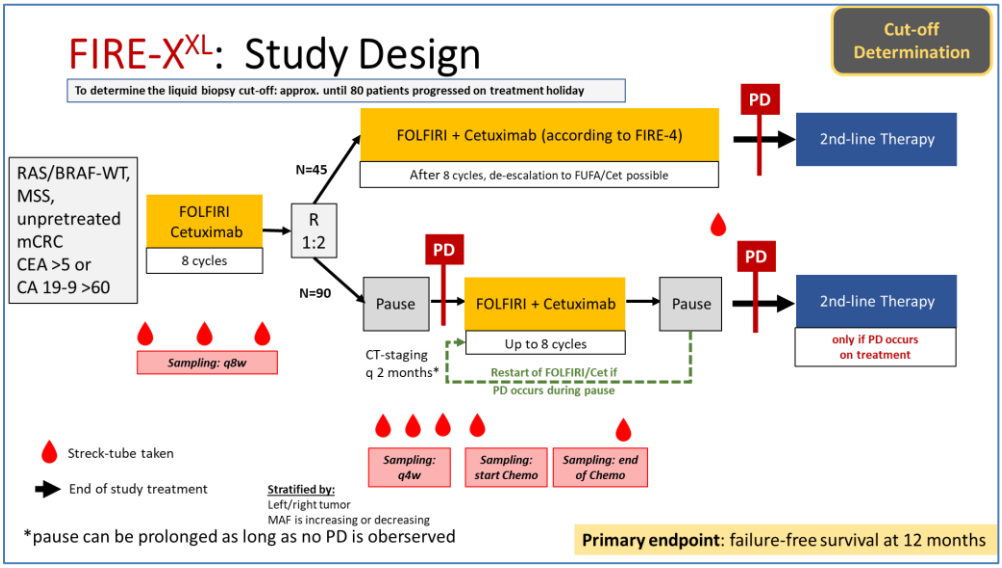
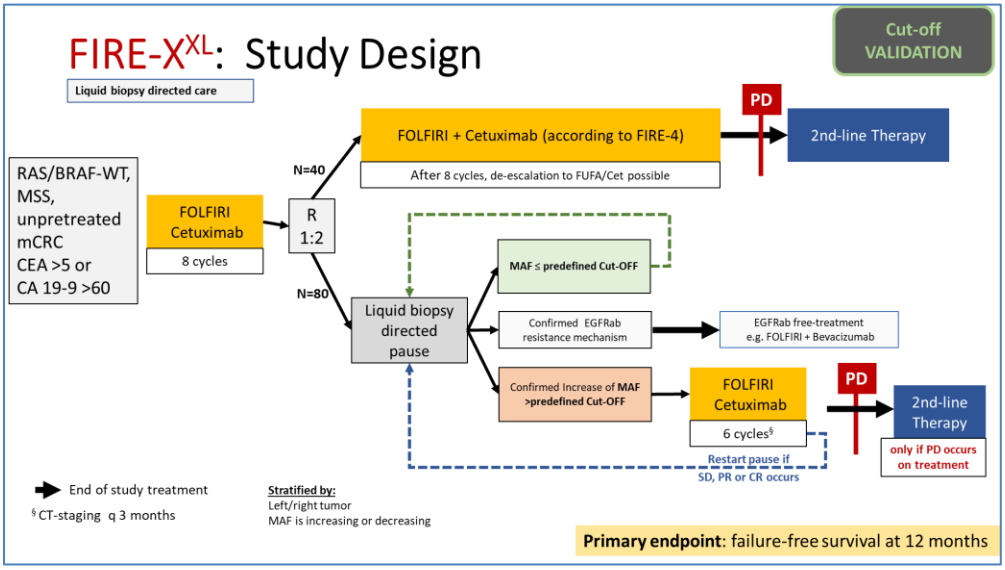
FIRE-XXL
Synopsis
-Confidential-

Title	**Randomized study to compare first-line treatment with either continuous or intermittent cetuximab plus FOLFIRI in patients with RAS/BRAF-wild-type metastatic colorectal cancer – FIRE-XXL**
Short title	FIRE-XXL
Sponsor	Charité Universitätsmedizin Berlin Charitéplatz1 10117 Berlin
Coordinating investigators	**Principal investigator:** Prof. Dr. med. Sebastian Stintzing Charité - Universitätsmedizin Berlin Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie am Campus Charité Mitte (CCM) Charitéplatz 1 10117 Berlin **Scientific Lead:** Prof. Dr. med. Volker Heinemann Klinikum der Universität München Medizinische Klinik und Poliklinik III Marchioninistraße 15 81377 München **Study coordination:** PD Dr. med. Arndt Stahler Charité - Universitätsmedizin Berlin Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie am Campus Charité Mitte (CCM) Charitéplatz 1 10117 Berlin
Protocol code	xxx
AIO trial-no.	xxx
EudraCT no	xxx
Protocol version and version date	Draft 0.1 of 23-SEP-2024
Investigational medicinal product(s)	none
Clinical trial phase	Randomized, open-label phase III
Number of patients	313 patients
Number of trial sites	About 60 trial sites

Indication studied	First-line treatment of negatively hyperselected RAS/BRAF wild-type metastatic colorectal cancer patients with left- and right-sided primary tumors
Background and rationale	The application of monoclonal antibodies directed against the epidermal growth factor receptor (EGFR) such as cetuximab in combination with cytotoxic regimens (e. g. FOLFIRI) has been established as preferred first-line regimen in RAS wild-type metastatic colorectal cancer (mCRC) patients [1]. Nevertheless, the continuous application of anti-EGFR targeted antibodies can leverage mutations associated with resistance at low allele frequencies, which disappear during the absence of anti-EGFR directed treatment [2, 3]. The multi-centre randomized phase II IMPROVE trial provided clinical validation on this molecular basis by improving the PFS on treatment for intermittent application of FOLFIRI plus panitumumab together with scheduled treatment pauses in mCRC patients compared to standard continuous treatment until disease progression or unacceptable toxicity [4]. Circulating tumour DNA (ctDNA) is a novel biomarker released by necrosis, apoptosis or active secretion by tumour cells, which has retrospectively been evaluated in the randomized phase III PARADIGM trial to optimize anti-EGFR treatment in mCRC patients and which indicated early radiologic disease progression during systemic treatment [5-7]. The FIRE-XXL trial aims to confirm superiority of intermittent versus continuous application of FOLFIRI plus cetuximab, to prospectively validate negative hyperselection of DNA mutations associated with resistance to anti-EGFR antibodies by ctDNA and to evaluate and validate a threshold value based on ctDNA increase to predict early disease progression in patients with RAS wild-type metastatic colorectal cancer. <u>Literature:</u> 1. Cervantes, A., et al., *Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up.* Annals of Oncology, 2023. **34**(1): p. 10-32. 2. Morelli, M.P., et al., *Characterizing the patterns of clonal selection in circulating tumor DNA from patients with colorectal cancer refractory to anti-EGFR treatment.* Ann Oncol, 2015. **26**(4): p. 731-6. 3. Parseghian, C.M., et al., *Anti-EGFR-resistant clones decay exponentially after progression: implications for anti-EGFR re-challenge.* Ann Oncol, 2019. **30**(2): p. 243-249. 4. Avallone, A. and A. Budillon, *Impact of Subsequent Therapies on Outcome of the FIRE-3/AIO KRK0306 Trial.* J Clin Oncol, 2016. **34**(13): p. 1564. 5. Siravegna, G., et al., *Integrating liquid biopsies into the management of cancer.* Nat Rev Clin Oncol, 2017. **14**(9): p. 531-548. 6. Tie, J., et al., *Circulating tumor DNA as an early marker of therapeutic response in patients with metastatic colorectal cancer.* Ann Oncol, 2015. **26**(8): p. 1715-22. 7. Vidal, J., et al., *Liquid Biopsy Detects Early Molecular Response and Predicts Benefit to First-Line Chemotherapy plus Cetuximab in Metastatic Colorectal Cancer: PLATFORM-B Study.* Clin Cancer Res, 2023. **29**(2): p. 379-388.
Objectives	**<u>Primary objectives</u>** • To demonstrate superior progression-free survival from randomization to progression on treatment (PFSot) in patients treated with FOLFIRI plus cetuximab in first-line mCRC for 8 cycles followed by a planned treatment

	pause and re-induction if progressive disease occurs during treatment holidays compared to continuous treatment. **Secondary objectives** • To assess efficacy and tumor response kinetics • To define and validate circulating tumor DNA (ctDNA) as screening and monitoring biomarker for response and resistance towards FOLFIRI plus cetuximab • To assess safety and tolerability • To assess quality of life during and after treatment **Translational research objectives** Identification and clinical/molecular characterization of patient subgroups with greatest or lowest benefit from respective treatment including efficacy and toxicity
Endpoints	**Primary endpoint** • PFS from randomization to progression on treatment (PFSot) **Secondary endpoints** **Efficacy** • PFS1 to PFSn (defined as each PFS from treatment start with FOLFIRI+cetuximab to the first disease progression in the respective treatment period) • Overall survival (OS) • Objective response rate (ORR) **Tumor response kinetics** • Dynamics of the tumor markers CEA and CA19-9 • Early tumour shrinkage • Depth of response **Circulating tumour DNA (ctDNA)** • Prospective validation to use ctDNA based RAS mutational analysis in addition to tissue-based RAS testing to exclude >5% RAS mutant cases from treatment • Define a cutoff in ctDNA change predicting progressive disease during treatment pause • Validate the formerly defined cutoff to induce re-use of FOLFIRI plus Cetuximab **Quality of life** • QoL as assessed with the QoL questionnaire EQ-5D-5L **Safety** • Type, incidence, severity, and causal relationship to IMPs of non-serious adverse events and serious adverse events (severity evaluated according to CTCAE version 5.0) **Translational endpoints** • DNA, mRNA and protein expression derived from FFPE tumor tissue and longitudinal blood samples • Integration of digital pathology using digitalized stained tumor tissue sections • Comprehensive data analysis using deep learning networks

Trial design	This is a multicentre, randomized phase III trial investigating the superiority of intermittent application of FOLFIRI plus cetuximab followed by a scheduled treatment pause compared to continuous treatment with FOLFIRI plus cetuximab until disease progression or unacceptable toxicity. This study is accompanied by a translational research program. Treatment is planned until progression, death or unacceptable toxicity. Patients are followed up with regard to survival and if applicable subsequent anti – cancer treatments until death or -after end of study treatment for at least 5 years after start of treatment, whichever date is earlier. The study is displayed in the following figures: Study schedule during Cut-off determination for the duration of the treatment holiday:  Study schedule during validation of the pre-determined cut-off determination for the duration of the treatment holiday: 

	Abbreviations: 5-FU = 5-fluorouracil
Inclusion criteria	- Patient's signed informed consent - Histologically confirmed, UICC stage IV unresectable adenocarcinoma of the colon or rectum - Locally confirmed RAS wild-type tumor status (KRAS and NRAS exon 2, 3, 4) - Age ≥18 at the time of written informed consent - ECOG performance status 0-1 - Presence of at least one measurable reference lesion according to the RECIST 1.1 criteria - Archival tumor tissue available - Consent to storage, molecular and genetic profiling of tumor material and blood - Adequate bone marrow function: o Leukocytes ≥ 3.0 x 10^9/L with neutrophils ≥ 1.5 x 10^9/L o Thrombocytes ≥ 100 x 10^9/L o Hemoglobin ≥ 8 g/dL) - Adequate hepatic function: o Serum bilirubin ≤ 1.5 x upper limit of normal (ULN) o ALAT and ASAT ≤ 2.5 x ULN (in the presence of hepatic metastases, ALAT and ASAT ≤ 5 x ULN) o INR < 1.5 and aPTT < 1.5 x ULN (patients without anticoagulation). Therapeutic anticoagulation is allowed if INR and aPTT have remained stable within the therapeutic range for at least 2 weeks. - Adequate renal function: o Creatinine clearance (calculated according to Cockcroft and Gault) ≥ 50 mL/min - Proficient fluorouracil metabolism as defined: o Prior treatment with 5-FU or capecitabine without unusal toxicity o If tested, normal DPD deficiency test according to the standard of the study site o 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% - Females of childbearing potential (FCBPs) and men must agree to use highly effective contraceptive measures (Pearl index <1) or practice true abstinence from any heterosexual intercourse (true abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject) for the duration of the study treatment and for at least 6 months after last administration of study medication. A woman will be considered as being of childbearing potential unless she is at least 50 years old and moreover has gone through menopause for at least 2 years or has been surgically sterilised. - 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	- Proof of a RAS mutation (KRAS or NRAS, exons 2, 3, 4 in the tumor (proven in the primary tumor or metastasis) or liquid biopsy (permitted only prior to Part 2) or absence of testing for RAS mutation - Previous chemotherapy for the colorectal cancer with the exception of adjuvant treatment, completed at least 6 months before entering the study. - New York Heart Association Class III or greater heart failure by clinical judgement. - Toxicity > Grade 1 that has not yet resolved, attributed to a previous (neo-)adjuvant treatment for colon or rectal cancer

	- Myocardial infarction, balloon angioplasty (PTCA) with or without stenting, and cerebral vascular accident/stroke within the past 12 months before randomization - Unstable angina pectoris - Unstable cardiac arrhythmia > grade 2 NCI CTCAE despite anti-arrhythmic therapy. - Active uncontrolled infection by investigator's perspective. - Pre-existing pulmonary fibrosis or immune pneumonitis - Additional cancer treatment (chemotherapy, radiation, immunotherapy or hormone treatment) during the study treatment in first-line and third-line treatment (treatments that are conducted as part of an anthroposophic or homeopathic treatment approach, e.g. mistletoe therapy does not represent an exclusion criterion) - Participation in a clinical study or experimental drug treatment within 30 days prior to study inclusion or within a period of 5 half-lives of the substances administered in a clinical study or during an experimental drug treatment prior to inclusion in the study, depending on which period is longest or simultaneous participation in another study while taking part in the study - Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, cetuximab, irinotecan and chemically related substances and/or hypersensitivity to any of the components in the formulations of the aforementioned substances, including known hypersensitivity reactions to monoclonal antibodies NCI CTC grade ≥ 3. - Known hypersensitivity to Chinese hamster ovary cell (CHO) –cellular products or other recombinant human or humanized monoclonal antibodies - Patients with known brain metastases or leptomeningeal disease. In case of clinical suspicion of brain metastasis a cranial CT or MRI must be performed to rule out brain metastasis before study inclusion. - History of acute or subacute intestinal occlusion, inflammatory bowel disease, immune colitis or chronic diarrhoea - Symptomatic peritoneal carcinosis - Severe, non-healing wounds, ulcers or bone fractures - Requirement for immunization with live vaccine including attenuated live vaccine from at least 4 weeks before start of study treatment until 6 months after the administration of chemotherapeutic substances. - Hemorrhagic diathesis or known thrombophilia - Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required) - Treatment with nucleoside analogues including sorivudine or brivudine within 28 days before study enrollment or requirement for concomitant antiviral treatment with sorivudine or brivudine or analogues - History of a second primary malignancy during the past 5 years before inclusion in the study or during participation in the study, with the exception of a basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ, if these were treated curatively. - Active alcohol or drug abuse - Any other severe acute or chronic concomitant disease or medical condition including psychiatric conditions (including recent i.e. within the past year or active suicidal ideation or behavior) or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. - Absent or restricted legal capacity
Treatment, dosage and administration	The regimen applied to both treatment arms is approved for first-line treatment of RAS wild-type mCRC and consists of a 14-day cycle. **<u>FOLFIRI plus cetuximab:</u>**

	Drug / **Dosage** / **Days given** Cetuximab: 400 mg/m² i.v. 250 mg/m² i.v. — 1, 8 or 500 mg/m² i.v. 120 min — 1 (Cycle 1) 500 mg/m² i.v. 60 min — 1 (from Cycle 2) Irinotecan: 180 mg/m² i.v. — 1 Folinic acid: 400 mg/m² i.v. — 1 5-Fluorouracil: 400 mg/m² bolus i.v. — 1 5-Fluorouracil: 2400 mg/m² i.v. — 1 Repeat d15 The two treatment arms differ in the application of FOLFIRI plus cetuximab: Arm 1: The patient will receive a standard regimen of FOLFIRI plus cetuximab, which may be de-escalated in case of toxicity at any time point if necessary and will be given until progression (PD). After 8 cycles (only in case of response to the regimen [CR and PR]) and after 12 cycles (in case of SD) the FOLFIRI regimen may be de-escalated according to investigator's discretion irrespective of occurrence of any toxicity. However, the patients must be administered cetuximab until the occurrence of progression. Arm 2: The patient will receive a standard regimen of FOLFIRI plus cetuximab for 8 cycles (16 weeks), at which time the first-line regimen will be stopped, and the planned treatment pause starts. At the occurrence of progression during treatment holiday, the initial regimen (FOLFIRI plus cetuximab) will be re-induced. The FOLFIRI plus cetuximab regimen may be de-escalated in case of toxicity if necessary according to investigator's discretion.
Statistical considerations	Hypothesis: This is a randomized, phase III trial, using a superiority design to investigate whether planed treatment holidays lead to a higher rate of on treatment progression free survival (PFSot) at 12 months using FOLFIRI plus Cetuximab after randomization in first-line, RASwt mCRC. For this purpose, 248 patients need to be randomized in a 2:1 fashion. It is assumed that FOLFIRI plus Cetuximab in the standard arm led to a PFSot rate after 12 months of 50% (FIRE-4 data). Furthermore, it is assumed that Arm 2 (planned treatment holidays with re-induction of FOLFIRI plus cetuximab if progression occurs during drug holiday) will achieve a PFSot rate of 68.5% (according to the IMPROVE Study (Avallone t al) Using a two group χ^2 test of equal proportions (odds ratio=1) (equal n's), 248 PFS events are required in order to detect a difference of 15% of PFSot rate with a power of 80% and a αerror of 5%. Therefore, patients need to be randomized with an assumed

	dropout rate of 21% including screening failures. Approximately a total of 313 patients need to be screened by liquid biopsy.	
Duration and end of trial	Estimated duration of the clinical trial: Planned first patient first visit: Planned recruitment period: Primary endpoint evaluable: Secondary endpoints evaluable Individual follow-up duration: End of trial:	appr.96 months Q1 2025 36 months LPI + 24 months (60 months in total) LPI + 60 months (96 months in total) After treatment end until death or for at least five years after start of treatment, whichever date is earlier Last Follow up visit of the last patient (LPLV)
GCP statement	The clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the applicable regulatory requirements.	