KURZPROTOKOLL
FIRE 4.5

Öffentlicher Titel	First-line FOLFOXIRI plus Cetuximab or FOLFOXIRI plus Bevacizumab bei metastasiertem Kolorektalkarzinom mit BRAF-Mutation
Wissenschaftl. Titel	Randomised study to investigate FOLFOXIRI plus cetuximab or FOLFOXIRI plus bevacizumab as first-line treatment of BRAF-mutated metastatic colorectal cancer (FIRE -4.5)
Kurztitel	FIRE 4.5
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, zweiarmig, Investigator Initiated Trial (IIT)
Studienphase	Phase II
Erkrankung	Verdauung: Darmkrebs (Kolorektales Karzinom): Erstlinie
Einschlusskriterien	- Histologically confirmed, UICC stage IV adenocarcinoma of the colon or rectum with metastases (metastatic colorectal cancer, mCRC), primarily non-resectable or surgery refused by the patient - RAS wild-type tumour status (KRAS and NRAS exons 2, 3, 4) (proven in the primary tumour or metastasis) - BRAF-mutated (V600E) tumour (proven in the primary tumour or metastasis) - Age >=18 years - ECOG performance status 0-1 - Patients suitable for chemotherapy administration - Patient's written declaration of consent obtained - Estimated life expectancy > 3 months - Presence of at least one measurable reference lesion according to the RECIST 1.1 – criteria (chest X-ray in two planes or chest CT and abdominal CT 4 weeks or less before randomisation) - Primary tumour tissue available and patient consents to storage and molecular and genetic profiling of the tumour material. Molecular profiling of blood samples is optionally performed. - Females of childbearing potential (FCBP) and men must agree to use effective contraceptive measures (Pearl index <1) for the duration of the study treatment and for at least 6 months after last administration of the study medication. A female subject will be considered to be of child-bearing potential unless she is >= 50 years of age as well as has had a natural menopause for at least 2 years or has been surgically sterilised - Adequate bone marrow function: (a) Serum bilirubin <= 1.5 x upper limit of normal (ULN); (b) ALAT and ASAT <= 2.5 x ULN (in case of hepatic metastases, ALAT and ASAT <= 5 x ULN) - 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: Serum creatinine <= 1.5 x ULN or creatinine clearance (calculated according to Cockcroft and Gault) >= 50ml/min. - Adequate cardiac function: ECG and echocardiogram with a LVEF of >=55% - No previous chemotherapy for metastatic disease (prior radiotherapy of metastasis/metastases without application of chemotherapy permitted provided that no radiated metastasis is selected as target lesion) - Time interval since last administration of any previous neoadjuvant/adjuvant chemotherapy or radiochemotherapy >=6 months - Any relevant toxicities of previous treatments must have subsided to grade 0
Ausschlusskriterien	- Grade III or IV heart failure (NYHA classification)

- Myocardial infarction, unstable angina pectoris, balloon angioplasty (PTCA) with or without stenting within the past 12 months before randomisation
- Pregnancy (absence of pregnancy has to be ascertained by a beta hCG test) or breast feeding
- Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study
- Additional cancer treatment (chemotherapy, radiation, immune therapy or hormone treatment) during the study treatment. Treatments that are conducted as part of an anthroposophical or homeopathic treatment approach, e.g. mistletoe therapy do not represent an exclusion criterion).
- Previous chemotherapy for the colorectal cancer with exception of chemotherapy or radiochemotherapy given as neoadjuvant or adjuvant treatment in curative treatment intention, completed >=6 months before entering the study.
- 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 clinical study while taking part in the study
- Known hypersensitivity or allergic reaction to any of the following substances: 5-fluorouracil, folinic acid, cetuximab, irinotecan, bevacizumab, oxaliplatin and chemically related substances and/or hypersensitivity to any of the excipients of any of the aforementioned substances
- Known hypersensitivity to CHO (Chinese hamster ovary cells) - cellular products or other recombinant human or humanised antibodies
- Patients with confirmed cerebral metastases. In case of clinical suspicion of brain metastases, a cranial CT or MRI must be performed to rule out brain metastases before study inclusion.
- History of acute or subacute intestinal occlusion or chronic inflammatory bowel disease or chronic diarrhoea.
- Symptomatic peritoneal carcinosis
- Severe, non-healing wounds, ulcers or bone fractures
- Patients with active infection (including confirmed HIV and/or HBV/HCV infection). In case of clinical suspicion of the presence of HIV or HBV/HCV infection, the latter should be ruled out before study inclusion.
- Requirement for immunisation with live vaccine during the study treatment.
- Uncontrolled hypertension
- Marked proteinuria (nephrotic syndrome)
- Arterial thromboembolism or severe haemorrhage within 6 months prior to randomisation (with the exception of tumour bleeding before tumour resection surgery)
- Haemorrhagic diathesis or tendency towards thrombosis
- Known DPD deficiency (specific screening not required)
- Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required)
- History of a second malignancy during the 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.
- Known history of alcohol or drug abuse

	- A significant concomitant disease, in particular chronic hepatic or renal disease, chronic inflammatory or autoimmune diseases, ruling out the patient's participation in the study according to investigatorßs judgement - Absent or restricted legal capacity
Alter	18 Jahre und älter
Molekularer Marker	KRAS wt BRAF
Prüfzentren	**Innere Medizin 1** (Geschlossen) Gastroenterologie / Hepatologie Theodor-Stern-Kai 7 60590 Frankfurt am Main Lisa Weiss Tel: 069 6301-87769 Fax: 069 6301-6580 Lisa.Weiss@unimedizin-ffm.de
Sponsor	Universitätsklinikum München
Förderer	Merck Serono
Registrierung in anderen Studienregistern	EudraCT 2015-004849-11