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Condition	Chemorefractory colorectal cancer
Primary aim of the study	Evaluation of patient related benefit of D-/L-methadone plus mFOLFOX6 compared to mFOLFOX6 alone in the treatment of patients with advanced colorectal cancer
Secondary aims of the study	• DCR 12 weeks after randomization (per protocol analysis) • Effect on tumor response according to RECIST 1.1 • Effect on progression free survival (PFS) • Effect on overall survival (OS) • Health related quality of life (EORTC QLQ-C30) • Patient-reported outcomes • Correlation of DCR, PFS, OS and tumor regression with pharmacogenomic markers, tumor biomarkers and molecular analyses (μ opioid receptor expression on tumor cells, ctDNA, transcriptome, miRNA-arrays) • Evaluation of the safety and tolerability profile. • Evaluation of the methadone levels under treatment • Correlation of μ opioid receptor expression in tumor tissue and efficacy
Study design	Phase I: 3+3 dose escalation study Phase II: Open-label, 2:1 randomized, controlled trial Patients in the mFOLFOX6 alone arm are allowed to cross over and receive methadone hydrochloride in combination with mFOLFOX6 upon disease progress
Study population	Patients with histologically confirmed, chemorefractory colorectal carcinoma
Sample Size	Phase I: At maximum 18 patients Phase II: 66 patients (44 / 22 patients as 2:1 randomized)
Therapy	Phase I: Step up with dose escalation of D,L-methadone hydrochloride in 3 cohorts (15 – 17,5 – 20 mg/bid orally) combined with mFOLFOX6 (day 1-3: Oxaliplatin 85mg/m² IV infusion, given as a 120 minutes IV infusion in 500 mL D5W, concurrent with leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²) IV infusion, followed by 46-hour 5-FU infusion (2400 mg/m²) Phase II: Continuous intake of pre-defined (phase I) D,L-methadone hydrochloride dose orally combined with mFOLFOX6 (day 1-3: Oxaliplatin 85mg/m² IV infusion, given as a 120 minutes IV infusion in 500 mL D5W, concurrent with leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²) IV infusion, followed by 46-hour 5-FU infusion (2400 mg/m²) compared to mFOLFOX6 alone

Primary endpoint	Disease control rate at week 12 after randomization
Secondary endpoints	Disease control rate 12 weeks after randomization (per-protocol-population), overall response rate according to RECIST 1.1, patient-reported outcomes, PFS, overall survival, quality of life, safety, correlation of μ opioid receptor expression in tumor tissue and efficacy.
Biometrics	The main outcome as the disease control rate at week 12 will be compared in a confirmatory fashion by a two-sided chi-square test at a significance level of 5%.
Time schedule	**Phase I:** First patient in to last patient out (months): at minimum 11 (3 cohorts), at maximum 22 (6 cohorts) Duration of the entire trial (months): at minimum 11 (3 cohorts), at maximum 22 (6 cohorts) Recruitment period (months): 9 Data evaluation and determination of recommended dose for phase II (months): 1 **Phase II:** First patient in to last patient out (months): 36 Duration of the entire trial (months): 36 Recruitment period (months): 24 Data evaluation and coverage (months): 12
Centers	Phase I: 3 national sites Phase II: 10 national sites
Main selection criteria	Inclusion criteria: • Advanced, histologically confirmed, metastatic colorectal carcinoma not suitable for resection and chemorefractory—~~or~~. Previously employed chemotherapy regimens and agents should comprise the following: Fluoropyrimidines, oxaliplatin, irinotecan, antiangiogenic agents (bevacizumab, aflibercept or ramucirumab), anti-EFGR-mAbs (in case of all-Ras-wildtype and left-sided primary tumor) and Trifluridin/Tipiracil (TAS102) • Microsatellite stable subset (MSS) of colorectal cancer • Prior antineoplastic therapy or radiochemotherapy is allowed up to two weeks prior to start of the study medication. However, for the phase II part of the trial, failure of this strategy must be confirmed. In case of prior radiotherapy/radiochemotherapy the target lesion used for tumor evaluation must not be in the radiation field. • There must be an oxaliplatin free period of at least 6 months prior to start of the study medication. • No polyneuropathy of > grade 1 • Tumor-related ECOG performance status 0-2 • Anticipated life expectancy ≥ 12 weeks • Creatinine clearance ≥ 30 ml/min • Serum total bilirubin level ≤ 3 x ULN. • ALT and AST ≤ 2.5 x ULN or ≤ 5.0 x ULN in the presence of liver metastasis (established after adequate biliary drainage) • White blood cell count ≥ 3.5 x 106/ml, neutrophil granulocytes count ≥ 1,5 x 106/ml, platelet count ≥ 100 x 106/ml • Pain must be controllable without the need of concomitant use of opioids including methadone • Signed informed consent according to ICH/GCP and national/local regulations (participation in translational research is obligate) • None of the following concomitant medications: MAO-B-Inhibitors, strong inductors or inhibitors of CYP3A4, antiarrhythmic drugs of class I and III or other drugs that have potential for QT-prolongation • Age ≥ 18 years

	• At least one measurable target lesion according to RECIST 1.1, Pre-irradiated or locally treated lesions must not be used as target lesions. Exclusion criteria: • Microsatellite unstable CRC (MSIhigh) • Chronic infectious diseases, immune deficiency syndromes • Polyneuropathy ≥ grade II according to CTCAE • Premalignant hematologic disorders, e.g. myelodysplastic syndrome • Disability to understand and sign written informed consent documents • Past or current history of malignancies except for the indication under this study and curatively treated: ▪ Basal and squamous cell carcinoma of the skin ▪ In-situ carcinoma of the cervix ▪ Other malignant disease without recurrence after at least 3 years of follow-up • Clinically significant cardiovascular disease (incl. myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment • History of or evidence upon physical examination of CNS disease unless adequately treated (e.g. primary brain tumor, seizure not controlled with standard medical therapy or history of stroke). • Pre-existing neuropathy > grade I (NCI CTCAE) • Severe non-healing wounds, ulcers or bone fractions • Evidence of bleeding diathesis or coagulopathy • Patients not receiving therapeutic anticoagulation must have an INR ≤ 1.4 and PTT ≤ 40 sec within 28 days prior to randomization. The use of full dose anticoagulants is allowed as long as the INR or PTT is within therapeutic limits (according to the medical standard of the institution) • Major surgical procedures or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgical procedure during the course of the study. • Pregnancy or breastfeeding women. • Use of cannabinoids because of possible overlap and /or potentiation of side effects • Concomitant daily use of opioids in the last 3 months including methadone prior start of study medication • Subjects with known allergies to the study drugs or to any of its excipients. • Treatment with another investigational drug or participation in another interventional trial (within the 14 days prior randomization or 5 plasma half-lifes of the used investigational drug, whatever is longer) • Any psychological, familial, sociological or geographical condition potentially compromising compliance with the study protocol and the follow-up schedule; those conditions should be discussed with the patient prior to registration in the trial