

AIO-KRK-0119: A phase I/II trial of D,L-Methadone and mFOLFOX6 in treatment of advanced colorectal cancer (MEFOX)

AIO-Studie

Studiennummer/-Code:	AIO-KRK-0119 / MEFOX		
Status:	in Rekrutierung		
Rekrutierungszeit:	Phase I:	von: Q2/2022 bis: Q4/2023	
	Phase II:	von: Q1/2024 bis: Q1/2026	
Anzahl Zentren:	geplant: 10	aktuell initiiert: 8	aktiv rekrutierend: 6
Weitere Zentren:	ja		
Anzahl Patienten:	geplant: 84	aktuell eingeschlossen: 4	
Letzte Aktualisierung	Oktober 2023		

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CONDITION	Chemorefractory colorectal cancer
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
PRIMARY OBJECTIVE	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 OBJECTIVES	<ul style="list-style-type: none"> • 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

EXPLORATORY OBJECTIVES	<ul style="list-style-type: none"> Correlation of μ opioid receptor expression to DCR and tumor response Assessment of responder or non-responder mutation signatures for mFOLFOX6 in combination with D,L-methadone in last-line patients
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.
INTERVENTION(S)	<p>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)</p> <p>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</p>
EXPLORATORY ANALYSIS / TRANSLATIONAL RESEARCH ENDPOINTS	<p>This trial provides the unique opportunity in colorectal cancer patients to obtain biomaterials after failure of all established therapeutic strategies for biomarker analysis and correlation with outcome. The participation in the translational research program of this study is compulsory. Core biopsies from the primary tumor or a metastatic site will be analyzed by immunohistochemistry with respect to the μ opioid receptor expression and expression data will be correlated with DCR and tumor response. Furthermore, blood samples will be taken at the EOT visit. ctDNA and exosomes will be extracted from blood samples, analyzed by exome sequencing and subjected to mutation analysis. The following questions shall be addressed: Are there responder or non-responder mutation signatures for mFOLFOX6 in combination with D,L-methadone in last-line patients? What are the pathways affected? Is there a correlation between μ opioid receptor expression and efficacy of the methadonemFOLFOX6 combination?</p>
BACKGROUND/RATIONALE	<p>There is no established standard of care for patients refractory to TAS102 (or regorafenib) as a last line therapy in mCRC, who are still eligible and willing to undergo therapy apart from the small group of patients with microsatellite instable tumors that benefit from PD1/PDL-1 inhibitors. This group of patients will be excluded from the trial. D,L-methadone showed promising data in some chemorefractory solid cancers (head and neck cancer, lung cancer, neuroblastoma, glioblastoma, bladder cancer and colorectal cancer in vitro in combination with chemotherapy.</p> <p>Data suggest that the combination of D,L-methadone with various chemotherapeutic agents including 5-FU and oxaliplatin can overcome chemoresistance and enable a renewed chemotherapy response. Data from the Friesen laboratory have shown that there is a synergy between D,L-methadone and oxaliplatin as well as 5-FU .</p> <p>The toxicity profile of oxaliplatin in combination with 5-FU, an established standard of care chemotherapy, is well known. D, L-methadone is used as a pain relieve medication with well-known side effects. The combination treatment is not expected to add novel, endangering or overlapping toxicities. The risk-benefit-assessment appears acceptable regarding the combinational use of these well-characterized drugs and the lack of established therapies. Overcoming chemoresistance is expected to result in better systemic tumor control.</p>
INCLUSION CRITERIA	<ol style="list-style-type: none"> Advanced, histologically confirmed, metastatic colorectal carcinoma not suitable for resection and chemorefractory or. Previously

	<p>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)</p> <ol style="list-style-type: none"> 2. Microsatellite stable subset (MSS) of colorectal cancer 3. 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 valuation must not be in the radiation field. 4. There must be an oxaliplatin free period of at least 6 months prior to start of the study medication. 5. No polyneuropathy of > grade 1 6. Tumor-related ECOG performance status 0-2 7. Anticipated life expectancy \geq 12 weeks 8. Creatinine clearance \geq 30 ml/min 9. Serum total bilirubin level \leq 3 x ULN. 10. ALT and AST \leq 2.5 x ULN or \leq 5.0 x ULN in the presence of liver metastasis (established after adequate biliary drainage) 11. White blood cell count \geq 3.5 x 10⁶/ml, neutrophil granulocytes count \geq 1,5 x 10⁶/ml, platelet count \geq 100 x 10⁶/ml 12. Pain must be controllable without the need of concomitant use of opioids including methadone 13. Signed informed consent according to ICH/GCP and national/local regulations (participation in translational research is obligate) 14. 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 15. Age \geq 18 years 16. At least one measurable target lesion according to RECIST 1.1, Preirradiated or locally treated lesions must not be used as target lesions.
<p>EXCLUSION CRITERIA</p>	<ul style="list-style-type: none"> • Microsatellite unstable CRC (MS high) • Chronic infectious diseases, immune deficiency syndromes • Polyneuropathy \geq 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 fractures • Evidence of bleeding diathesis or coagulopathy • Patients not receiving therapeutic anticoagulation must have an INR \leq 1.4 and PTT \leq 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.

	<ul style="list-style-type: none"> • 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-life 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
TRIAL DURATION	<p>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</p> <p>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</p>
SAMPLE SIZE ESTIMATION	<p>The sample size calculation for the phase-II study is based on a disease control rate (DCR) 12 weeks after randomization in a group of patients treated with 5-FU/Oxaliplatin reintroduction of 39% [2]. By applying D,L-methadone plus mFOLFOX6 it is assumed, that the rate can be doubled to 80%. Using a chi-square-test (two-sided, significance level 5%, 80% power) for sample size calculation, a total sample size of n=49 is required. The 2:1 randomization results in a sample size of n=33 for arm A and n=16 in arm B (nQuery Advanced 8.1) for this difference in rates.</p> <p>Clinical experience gives an estimate for drop-out of 25%, resulting in a total sample size of 66 patients (arm A: n=44, arm B: n=22).</p>
PARTICIPATING CENTERS	<p>Phase I: 3 national sites Phase II: 10 national sites</p>
FURTHER CENTERS DESIRED?	yes
NUMBER OF PATIENTS	<p>Phase I: At maximum 18 patients Phase II: 66 patients (44 / 22 patients as 2:1 randomized)</p>