KURZPROTOKOLL
AIO-KRK-0214

Öffentlicher Titel	Phase II Studie zu neoadjuvanter Chemotherapie und Aflibercept bei Rektumkarzinom im Stadium T3
Wissenschaftl. Titel	mFOLFOX6 vs. mFOLFOX6 + aflibercept as neoadjuvant treatment in MRI-defined T3-rectal cancer: a randomized phase-II-trial
Kurztitel	AIO-KRK-0214
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, zweiarmig, Investigator Initiated Trial (IIT)
Studienphase	Phase II
Erkrankung	Verdauung: Darmkrebs (Kolorektales Karzinom): neoadjuvant
Einschlusskriterien	- Age >= 18 years on day of signing informed consent - Signed and dated informed consent, and willing and able to comply with protocol requirements - WHO/ECOG Performance Status (PS) 0-1 - Diagnosis of rectal adenocarcinoma - Candidate for sphincter-sparing surgical resection prior to neoadjuvant therapy according to the primary surgeon, i.e. no patient will be included for whom surgeon indicates need for abdomino-perineal resection (APR) at baseline. - Clinical staging is based on the combination of the following assessments: (a) Physical examination by the primary surgeon; (b) CT scan of the chest/abdomen; (c) Pelvic MRI; (d) Rigid rectoscopy / endoscopic ultrasound (ERUS); (e) Both examinations (MRI + ERUS) are mandatory - The tumor has to fulfill the following criteria: (a) No symptomatic bowel obstruction; (b) Locally advanced rectal and rectosigmoid cancer, i.e. lower border of tumor > 5 cm and < 16 cm from anal verge as determined by rigid rectoscopy; (c) - MRI criteria: (c1) Lower border of tumor below a line defined by promontorium and symphysis, regardless of the criterion “< 16 cm from anal verge as determined by rigid rectoscopy”; (c2) No evidence that tumor is adjacent to (defined as within 2 mm of) the mesorectal fascia on MRI (i.e. CRM > 2 mm); (c3) Only T3-tumors are included, i.e infiltration into perirectal fat < 10 mm provided CRM > 2 mm; (c4) Note: MRI criteria are used for the definition of T3 tumor (i.e. exclusion of T2 and T4 situation). - Hematological status: (a) Neutrophils (ANC) >= 2 x 10e9/L; (b) Platelets >= 100 x 10e9/L; (c) Hemoglobin >= 9 g/dL (previous transfusion of packed blood cells allowed) - Adequate renal function: (a) Serum creatinine level <= 1.5 x upper limit normal (ULN) or <=1.5 mg/dl; (b) Creatinine clearance >= 30 ml/min - Adequate liver function: (a) Serum bilirubin <= 1.5 x upper limit normal (ULN) Alkaline phosphatase < 3 x ULN; (b) AST and ALT < 3 x ULN - Proteinuria < 2+ (dipstick urinalysis) or <= 1 g/24 hour or <= 500 mg/dl - Regular follow-up feasible - For female patients of childbearing potential, negative pregnancy test within 1 week (7 Days) prior of starting study treatment

- Female patients of childbearing potential (i.e. did not undergo surgical sterilization – hysterectomy, bilateral tubal ligation, or bilateral oophorectomy - and is not post-menopausal for at least 24 consecutive months) must commit to using highly effective and appropriate methods of contraception until at least 6 months after the end of study treatment such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), vasectomized partner, bilateral tubal occlusion, sexual abstinence. If an oral contraception is used, a barrier method of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge) has to be applied additionally.
- Fertile male patients with a partner of childbearing potential must commit to using highly effective and appropriate methods of contraception (details see above) until at least 9 months after the end of study treatment.

Ausschlusskriterien

- Distant metastases (CT scans of thorax and abdomen are mandatory)
- cT2 and cT4 tumors (defined by MRI criteria)
- Exclusion of potentially compromised CRM as defined by MRI criteria (i.e. > 2 mm distance from CRM)
- Prior antineoplastic therapy for rectal cancer
- History or evidence upon physical examination of CNS metastasis
- Uncontrolled hypercalcemia
- Pre-existing permanent neuropathy (NCI-CTCAE grade >= 2)
- Uncontrolled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg), or history of hypertensive crisis, or hypertensive encephalopathy
- Concomitant protocol unplanned antitumor therapy (e.g. chemotherapy, molecular targeted therapy, immunotherapy, radiotherapy)
- Treatment with any other investigational medicinal product within 28 days prior to study entry
- Known dihydropyrimidine dehydrogenase (DPD) deficiency
- Treatment with CYP3A4 inducers unless discontinued > 7 Days prior to randomization
- Any of the following in 3 months prior to inclusion: (a) Grade 3-4 gastrointestinal bleeding; (b) Treatment resistant peptic ulcer disease; (c) Erosive esophagitis or gastritis; (d) Infectious or inflammatory bowel disease; (e) Diverticulitis
- Any active infection within 2 weeks prior to study inclusion
- Vaccination with a live, attenuated vaccine within 4 weeks prior to the first administration of the study medication
- Other concomitant or previous malignancy, except: (a) Adequately treated in-situ carcinoma of the uterine cervix; (b) Basal or squamous cell carcinoma of the skin; (c) Cancer in complete remission for > 5 years
- Any other serious and uncontrolled non-malignant disease, major surgery or traumatic injury within the last 28 days prior to study entry
- Pregnant or breastfeeding women
- Patients with known allergy to any constituent to study drugs
- History of myocardial infarction and/or stroke within 6 months prior to randomization, NYHA class III and IV congestive heart failure
- Severe renal insufficiency (creatinin clearance < 30 ml/min)
- Bowel obstruction

- Contra-indication to the assessment by MRI
- Involvement in the planning and/or conduct of the study (applies to both Sanofi staff and/or staff of Sponsor and study site)
- Patient who might be dependent on the sponsor, site or the investigator
- Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
- Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].

Alter	18 Jahre und älter
Sponsor	AIO-Studien GmbH
Förderer	Sanofi Aventis GmbH
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT03043729 EudraCT 2015-002773-38